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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2022

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number 001-38899

Milestone Pharmaceuticals Inc.

(Exact name of registrant as specified in its charter)

Québec	**Not applicable**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
1111 Dr. Frederik-Phillips Boulevard, Suite 420 Montréal, Québec CA	**H4M 2X6**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code **(514)-336-0444**

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Shares	MIST	The Nasdaq Stock Market LLC

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically, if any, every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer", "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐	Accelerated filer ☐	Non-accelerated filer ☒	Smaller reporting company ☒	Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C 7262(b)) by the registered public accounting firm that prepared or issued its audit report. Yes ☐ No ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b).☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value (approximate) of the registrant's common equity held by non-affiliates based on the closing price of a share of the registrant's common share for The Nasdaq Stock Market on June 30, 2022 (the last business day of the registrant's most recently completed second fiscal quarter) was $184.5 million.

As of March 29th, 2023, the total number of shares outstanding of the registrant's Common Shares was 33,287,226 shares, net of treasury shares.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive proxy statement for the registrant's 2023 annual meeting of stockholders, to be filed within 120 days after the close of the registrant's fiscal year, are incorporated by reference into Part III of this Annual Report.

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This Annual Report on Form 10-K contains references to United States dollars and Canadian dollars. All dollar amounts referenced, unless otherwise indicated, are expressed in United States dollars. References to “$” are to United States dollars and references to “C$” are to Canadian dollars.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of known and unknown risks, uncertainties and assumptions, including risks described in the section titled "Risk Factors" and elsewhere in this Annual Report on Form 10-K, regarding, among other things:

- the initiation, timing, progress and results of our current and future clinical trials of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of paroxysmal supraventricular tachycardia, our Phase 2 clinical trial of etripamil for the treatment of atrial fibrillation and rapid ventricular rate, and of our research and development programs;
- uncertain impacts that public health crises may have on our business, strategy, clinical trial progress and research and development efforts;
- our ability to develop and, if approved by regulatory authorities, commercialize etripamil in China and Taiwan through our license agreement with Ji Xing Pharmaceuticals;
- our plans to develop and commercialize etripamil and any future product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to successfully acquire or in-license additional product candidates on reasonable terms;
- our ability to establish collaborations or obtain additional funding;
- our ability to obtain regulatory approval of our current and future product candidates;
- our expectations regarding the potential market size and the rate and degree of market acceptance of etripamil and any future product candidates;
- our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources;

- the implementation of our business model and strategic plans for our business, etripamil and any future product candidates;
- our intellectual property position and the duration of our patent rights;
- developments or disputes concerning our intellectual property or other proprietary rights;
- our expectations regarding government and third-party payor coverage and reimbursement;
- our ability to compete in the markets we serve;
- the impact of government laws and regulations;
- developments relating to our competitors and our industry; and
- the factors that may impact our financial results.

The foregoing list of risks is not exhaustive. Other sections of this Annual Report on Form 10-K may include additional factors that could harm our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements.

In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur at all. You should refer to the section titled "Risk Factors" for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise. The Private Securities Litigation Reform Act of 1995 and Section 27A of the Securities Act of 1933, as amended, or the Securities Act, do not protect any forward-looking statements that we make in connection with this Annual Report on Form 10-K.

SUMMARY OF RISK FACTORS

Our business is subject to numerous risks and uncertainties, including those described in Item 1A "*Risk Factors*". These risks include, but are not limited to the following:

- We have incurred significant operating losses since inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future and may never achieve or maintain profitability.
- We will require substantial additional funding to finance our operations. If we are unable to raise capital when needed, we could be forced to delay, reduce or terminate our development of etripamil or other operations.
- Raising additional capital may cause dilution to our shareholders, restrict our operations or require us to relinquish rights to our product candidates.
- Economic uncertainty, including related to inflation, may adversely affect our results of operations.
- We have only one product candidate, etripamil, for which we are currently pursuing clinical development. Our future success is substantially dependent on the successful clinical development and regulatory approval of etripamil. If we are not able to obtain required regulatory approvals for etripamil or any future product candidates, we will not be able to commercialize etripamil or any future product candidates and our ability to generate revenue will be adversely affected.
- We may not be successful in our efforts to expand our pipeline of product candidates beyond etripamil for paroxysmal supraventricular tachycardia.
- The development of additional product candidates is risky and uncertain.
- Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and we cannot assure you that any ongoing, planned or future clinical trials will lead to results sufficient for the necessary regulatory approvals.
- Our business, operations and clinical development timelines and plans have been adversely affected by the effects of health epidemics, and could be affected by future health epidemics.
- We may encounter substantial delays or difficulties in our clinical trials.
- Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be delayed, made more difficult or rendered impossible by multiple factors outside our control.
- If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell etripamil or any future product candidates, we may not be successful in commercializing etripamil or any future product candidates, if and when they are approved.
- Even if etripamil or any future product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.
- Even if we successfully obtain approval for etripamil, its success will be dependent on its use in accordance with labeled instructions for use.
- If the market opportunities for etripamil and any future product candidates are smaller than we estimate, our business may suffer.
- Coverage and adequate reimbursement may not be available for etripamil or any future product candidates, which could make it difficult for us to gain market acceptance.
- Even if we obtain and maintain approval for etripamil or any future product candidates from the Food and Drug Administration, or FDA, we may never obtain approval of etripamil or any future product candidates outside of the United States, which would limit our market opportunities and could harm our business.
- Even if we obtain regulatory approval for etripamil or any future product candidates, they will remain subject to ongoing regulatory oversight.
- We will rely on third parties to produce clinical and commercial supplies of etripamil and any future product candidates.
- We rely on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.
- Etripamil is intended to be used with a nasal-spray device, which may result in additional regulatory and supply risks.

- If we are unable to obtain and maintain patent protection for etripamil or any future product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs similar or identical to ours, and our ability to commercialize successfully our product candidates may be impaired.
- Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.
- The market price of our common shares has been and may continue to be volatile and fluctuate substantially, and you could lose all or part of your investment.
- Our common shares are thinly traded and our shareholders may be unable to sell their shares quickly or at market price.
- Concentration of ownership of our common shares among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

PART I

ITEM 1. BUSINESS

Company Overview

We are a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. Our lead product candidate etripamil is a novel and potent calcium channel blocker that we designed as a rapid-onset nasal spray to be self-administered by patients. We are developing etripamil for the treatment of specific arrhythmias with a lead indication to treat paroxysmal supraventricular tachycardia, or PSVT, and a subsequent indication to treat atrial fibrillation with rapid ventricular rate, or AFib-RVR.

PSVT is a highly symptomatic and impactful heart arrhythmia characterized by unpredictable attacks of a racing heart, often exceeding 150 beats per minute. Symptoms of PSVT often arise suddenly and include palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting, and anxiety, causing many patients to interrupt their daily activities at the time of symptom-onset. The impact and morbidity from an episode of PSVT can be especially detrimental in patients with underlying cardiovascular or medical conditions, such as heart failure, obstructive coronary disease, or dehydration. The uncertainty of when such an attack of PSVT will strike or how long it will persist is anxiety-provoking, reduces patients' quality of life and prevents participation in many desired activities. Drugs approved for the treatment of PSVT attacks include adenosine, verapamil, and diltiazem, with all being administered intravenously under medical supervision, usually in the emergency department. Other oral drugs are sometimes used to treat attacks in a concept called "pill in the pocket." However, those drugs have never been proven effective or safe and are not approved for this use. Doctors are frustrated by the lack of effective treatment options besides a prolonged, unpleasant, and costly trip to the emergency department or, for some patients, an invasive ablation procedure. PSVT is traumatic for patients, frustrating for healthcare providers, and costly for payers. With no pharmaceutical innovation in the treatment of PSVT for over 30 years and a movement in the healthcare system to enable patient centered care, there is an opportunity to help patients living with PSVT to take greater control over their PSVT attacks.

Atrial Fibrillation, or AFib, is a common form of arrhythmia with an irregular and often rapid heart rate that is often markedly symptomatic and, without proper treatment, can increase the risk of stroke, heart failure, and other cardiovascular complications. A common complication of AFib is a rapid ventricular rate, or AFib-RVR, which is frequently defined as a heart rate $\geq$ 110 beats per minute. The occurrence of a rapid ventricular rate in patients with atrial fibrillation increases the likelihood of symptoms including heart palpitations, shortness of breath and weakness. There are two commonly used pharmacological approaches to chronically manage AFib, rhythm control and rate control. Regardless of the chronic approach, when faced with an episode of AFib-RVR, acute rate control is called for most commonly in the form of oral AV-nodal targeted drugs such as a beta blocker or calcium channel blockers. However, these oral rate control drugs, when used acutely, do not adequately provide immediate ventricular rate control due to a 30- to 60-minute delayed onset of action, and, as a result, many patients seek faster and more certain rate reduction and symptom resolution by going to the emergency department for acute treatment utilizing intravenous rate control and/or electrical cardioversion of their atrial fibrillation. Similar to PSVT, patients feel a loss of control by needing to visit the emergency department for overcoming

their atrial fibrillation attack, doctors are frustrated by the lack of options for patients to self-manage these acute rate attacks and payer organizations would prefer to treat the AFib-RVR attacks in a more cost effective and time-efficient manner.

Our objective is to develop and commercialize etripamil as a fast-acting nasal spray to be prescribed by the doctor so that the patient can carry etripamil with them for use wherever and whenever an attack occurs. We have completed patient conduct (last patient last visit) in the Phase 3 clinical trials for the lead indication and we plan to submit a New Drug Application, or NDA, for marketing approval in the United States for etripamil for the treatment of PSVT mid-2023. If approved, we believe that etripamil will provide the patient with a portable treatment to stop an attack at-home and to reduce the reliance on the emergency department. We believe that this may help patients to live their lives with less concern over when their next PSVT attack will occur. For health care providers, etripamil could represent a new tool they can offer to their patients to better self-manage their PSVT attacks resulting in fewer calls to their office, a more efficient use of healthcare resources, and more empowered, satisfied patients.

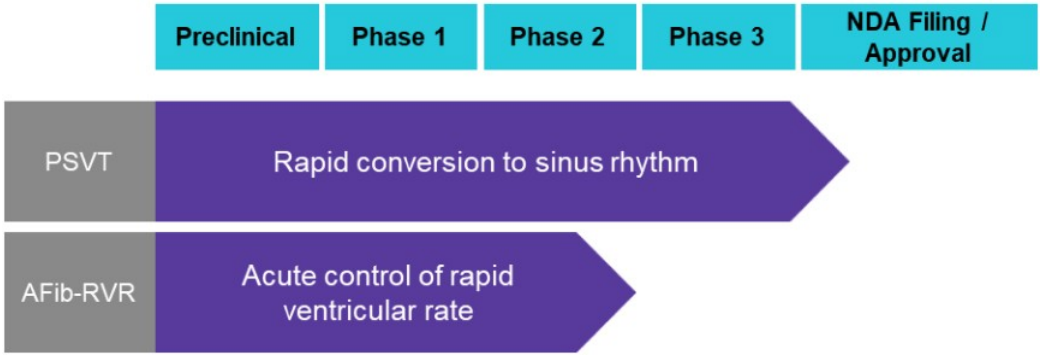
Etripamil is currently in Phase 2 clinical development for assessing its safety and effectiveness in AFib-RVR. Similar to our approach for PSVT, we believe that etripamil has the potential to help the patient experiencing a symptomatic episode of AFib-RVR to self-manage their condition by conveniently, reliably and quickly reducing their elevated heart rate wherever and whenever the episode occurs, thereby reducing the need for emergency department utilization that many patients currently seek.

We believe that PSVT is a large and under-recognized market that we estimate affects approximately two million Americans and results in over 150,000 emergency department visits and hospital admissions and up to 80,000 ablations per year. From this diagnosed population, we define the target addressable market for etripamil as the 40 to 60% of patients who experience frequent and longer, moderate to severe episodes each year. After being exposed to the data from the RAPID clinical study in market research, Cardiologists reported a willingness to prescribe etripamil to approximately 50% of the patients with PSVT in their care, which suggests 500,000 to 800,000 patients can potentially be treated with etripamil in the peak year. Additionally, we believe that these target patients will use etripamil to treat a median of five episodes per year based on the projected number of longer or more intense episodes (self-reported) experienced by the patient. This implies demand in the US for etripamil of 2.5 million to 4 million episodes treated in the peak year.

The American Heart Association estimates a prevalence for AFib of seven million by 2030, while the Centers for Disease Control (CDC) reports this prevalence as increasing to 12 million over the same time period. According to the Healthcare and Utilization Project, AFib resulted in 660,000 patient visits to the emergency department and 465,000 admissions to the hospital in 2016. From market research we estimate the target addressable market for etripamil in patients with AFib and rapid ventricular rate (RVR) as approximately 30 to 40% of the diagnosed prevalent population, defined as patients experiencing at least one symptomatic episode of AFib-RVR requiring treatment per year.

Our Pipeline

The figure below sets forth the status and focus of etripamil:



PSVT Phase 3 Program Highlights: The RAPID, NODE-301, NODE-302, and NODE-303 Trials

On October 17, 2022, we announced positive and statistically significant topline efficacy and safety data from the Phase 3 RAPID clinical trial of etripamil in patients with PSVT. These results were further presented shortly thereafter, on November 7, 2022, as a Late-Breaking Clinical Trial at the American Heart Association Scientific Meetings (Chicago, IL). RAPID, our multi-center, randomized, double-blind, placebo-controlled, event-driven Phase 3 trial, enrolled 706 patients across clinical sites in North America and Europe. Patients were randomized 1:1 to a regimen of self-administering a first dose etripamil nasal spray, with a repeat dose 10 minutes later if symptoms persisted, or a matching placebo regimen. Self-administration was prompted by a patient's customary symptoms and was performed in the at-home setting without medical supervision. The RAPID trial achieved its primary endpoint, with patients taking the etripamil regimen demonstrating a highly statistically significant and clinically meaningful difference in time to SVT conversion as compared to placebo. A Kaplan Meier analysis demonstrated a significantly greater proportion of patients who took etripamil converted within thirty minutes compared to placebo (64.3% vs. 31.2%; hazard ratio, or HR, 2.62; 95% CI 1.66, 4.15; $p<0.001$). By 90 minutes post-study drug administration, 80.6% of etripamil patients converted versus 60.7% of placebo patients (HR = 1.93; 95% CI 1.349, 2.752; $p<0.001$) and statistical significance was maintained throughout the 5-hour observation window. Statistically significant reductions in time to conversion in patients who took etripamil were evident early and persisted throughout the observation window of the study compared to placebo. The median time to conversion for patients in RAPID who self-administered etripamil was 17.2 minutes compared to 53.3 minutes for patients on placebo. The safety and tolerability data from the RAPID trial continue to support the potential self-administration use of etripamil, with findings consistent with those observed in prior trials. The most common randomized-treatment emergent adverse events, or RTEAEs, adverse events, or AEs, which occurred within 24 hours of etripamil administration, were related to the nasal local administration site. Overall, the majority of RTEAEs were reported as mild (68%) or moderate (31%). There were no serious AEs related to etripamil.

The use of additional medical interventions and emergency department utilization were important secondary measures of efficacy for both the RAPID and NODE-301 studies, although with the understanding that neither study was individually powered to expect statistical differences. In a pre-planned analysis across both studies, patients who self-administered etripamil sought additional medical interventions 43% less frequently (15% vs. 25%; $p=0.013$) and had 39% fewer emergency department visits (14% vs. 22%; $p=0.035$) than patients in the placebo arm.

NODE-303 is a Phase 3, multi-center, open-label safety trial, evaluating primarily the safety of etripamil when self-administered without medical supervision over multiple, separate SVT episodes. After consultation with the regulatory authorities, it was concluded that the test doses procedure was an unnecessary step for the self-administration of etripamil and it was removed from the requirements of the NODE-303 safety study. The NODE-303 trial was initiated with an etripamil 70 mg single-dose regimen and the 70 mg optional repeat-dose regimen was introduced into the trial starting in the second half of 2021 following FDA acceptance of the protocol amendment. The trial was sized in order to add to the safety data from the remainder of the development program, including those data already obtained from the RAPID, NODE-301 and NODE-302 trials, in order to fulfill the safety and exposure dataset needed for NDA filing. Following the results from the RAPID study, initially obtained in October 2022, and the assessment of the total exposures to etripamil in the development program to date, we believe we have the safety dataset needed for review of the NDA for PSVT and have moved to the closure stage of the NODE-303 study.

We are conducting patient access programs to provide further access to etripamil to patients who have participated in the clinical development registration trials to treat their future SVT episodes. These programs are tailored to meet the regulatory requirements in the territories in which the clinical sites are located.

The NODE-301 trial is a placebo-controlled Phase 3 safety and efficacy trial and the first trial ever conducted to treat attacks of PSVT in the at-home setting. NODE-301 enrolled 431 patients across 65 sites in the United States and Canada. Although the study did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five-hour period following study drug administration in which patients wore a cardiac monitor, both prespecified and post hoc analyses at earlier time periods, namely at 30 minutes, showed significant treatment effects in favor of etripamil. For example, in a post hoc analysis of the NODE-301 data, 54% of etripamil patients vs. 35% of placebo patients converted within 30 minutes (HR 1.87, p=0.02). The safety and tolerability data from the NODE-301 trial support the potential self-administration use of etripamil, with the most common randomized treatment emergent adverse events, or RTEAEs, adverse events, or AEs, which occurred within 24 hours of etripamil administration, being related to the nasal local administration site. Overall, the majority of RTEAEs were reported as mild (85%) to moderate (15%). There were no serious AEs related to etripamil. After reviewing the data from NODE-301 with the FDA in July 2020, the Agency indicated that an analysis period shorter than 5 hours would be appropriate to measure the efficacy of etripamil. The FDA indicated that two trials, the RAPID and NODE-301 trials could potentially fulfill the efficacy requirement for our planned NDA for etripamil in patients with PSVT, both using time to conversion over the first 30 minutes with a target p-value of less than 0.05 as the primary endpoint.

NODE-302 is a Phase 3 multi-center, open-label safety extension of the NODE-301 trial. Patients who completed NODE-301 and enrolled in NODE-302 could administer open-label drug for up to an additional 11 episodes of PSVT. The study's objective is to evaluate the safety of etripamil nasal spray when self-administered by patients without medical supervision for spontaneous episodes of SVT in an outpatient setting over recurrent episodes. While the primary purpose of the trial is safety, efficacy assessments were also performed. We presented data from the NODE-302 study at a late-breaking session of the Heart Rhythm Society's Heart Rhythm 2022 Annual conference. Of 198 eligible NODE-301 patients, 169 (85%) enrolled in NODE-302 and 105 (62%) experienced a perceived episode of PSVT, self-administered etripamil and were included in the safety population. Overall, the rate of conversion of PSVT to normal sinus rhythm at 30 minutes following etripamil administration was 60.2% with a median time to conversion of 15.5 minutes (95% CI, 11.3-22.1 minutes), findings consistent with those from other studies, even those of a different design, indicating robustness of results. Among 40 patients who self-treated two separate episodes, 21 of 26 (81%) who converted on their first episode were also successfully converted on their second episode. Moreover, the need for an external medical intervention (e.g., an intravenous therapy administered in an emergency department) to terminate a PSVT episode was low (13% of patients and 8.5% of positively adjudicated PSVT episodes). Etripamil was generally well-tolerated, with adverse events consistent with those observed in previous trials; most adverse events related to treatment were localized to the nasal administration site and were mild and transient.

AFIB RVR Phase 2 Proof of Concept Trial: Reduction of Ventricular Rate in Patients with Atrial Fibrillation (ReVeRA)

The Phase 2, double-blind, placebo-controlled, proof-of-concept study, Reduction of Ventricular Rate in Patients with Atrial Fibrillation (ReVeRA), in patients with atrial fibrillation with rapid ventricular response (AFib/RVR), is being conducted in Canada and the Netherlands in collaboration with the Montreal Heart Institute, the WCN network, and other research centers. The ReVeRA study is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo to patients presenting with symptomatic AFib/RVR. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect. The trial is being conducted in the emergency department setting under medical supervision.

Our Strategy

Our goal is to identify, develop and commercialize innovative cardiovascular medicines, including etripamil for the treatment of PSVT, AFib-RVR and other cardiovascular indications, and additional clinical stage compounds for other cardiovascular conditions. The key elements of our business strategy to achieve this goal include the following:

- ***Successfully complete development and obtain regulatory approval of etripamil for the treatment of PSVT.*** We are focused on efficiently developing and obtaining approval for etripamil to treat patients with PSVT. We intend to first seek regulatory approval in the United States, followed by Europe and other major markets.

- ***Expand the scope of cardiovascular indications for etripamil beyond PSVT.*** We are investigating, in a Phase 2 proof of concept study, the use of etripamil for the treatment of patients with AFib-RVR. We believe that etripamil could benefit patients with AFib-RVR based on the approved use of intravenous, or IV, calcium channel blockers in this indication. We are also exploring the additional cardiovascular opportunities for the use of etripamil.

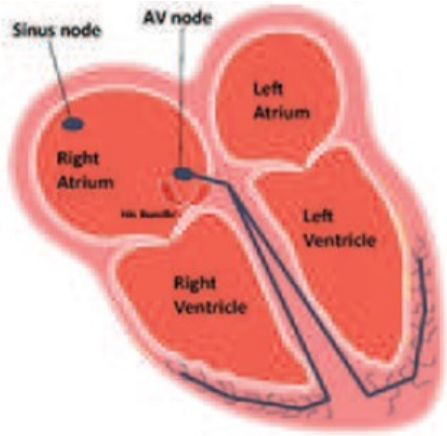
- ***Maximize the value of our programs by maintaining flexibility to commercialize our product candidates independently or through collaborative partnerships.*** We currently have exclusive development and commercialization rights for etripamil for our initial indications of PSVT and AFib-RVR. We are establishing commercialization and marketing capabilities with a focus to commercialize etripamil in the United States. Outside of the United States, we are considering commercialization strategies that may include collaborations with other companies.

- ***Leverage our expertise and experience to expand our pipeline of product candidates.*** We seek to maximize our commercial opportunities by acquiring or in-licensing product candidates for indications with significant unmet need with a focus on novel treatments for cardiovascular or other conditions. Our leadership team has extensive experience in developing and commercializing successful drugs. We intend to leverage the collective talent within our organization and our network to guide our development plans and pipeline expansion.

Cardiac and Pharmacologic Basis of Development Programs

Normal Conduction

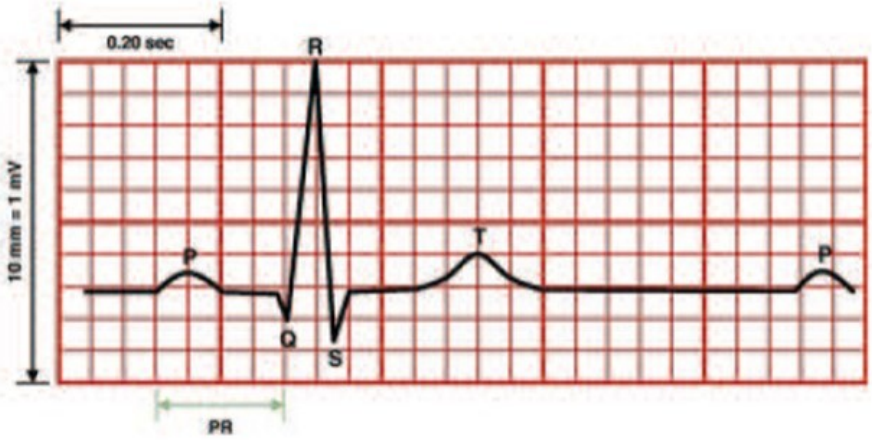
Within the right atrium, one of the heart's upper chambers, sits a specialized structure called the sinus node. The sinus node, serving as the heart's intrinsic pacemaker, generates an electrical signal which spreads throughout both atria and then is transmitted down to the lower chambers, the ventricles, via another specialized electrical tissue, the atrio-ventricular, or AV, node, which is shown in the figure below. Upon reaching the ventricles, the electrical signal them to contract, pumping blood out to the lungs and the rest of the body. Another heartbeat does not occur until a new signal is generated from the sinus node and the cycle repeats. Under normal conditions, passage from the sinus node over the AV node is the only way for the electrical impulse to travel from the atria down to the ventricles.



The electrical signal of each heartbeat can be detected by placing sensors known as electrodes over the skin, and recorded over time in a tracing known as an electrocardiogram, or ECG. The ECG measures signal voltage and duration. To the trained interpreter, an ECG conveys a large amount of information about the structure and function of the heart, including among other things, heart rate and rhythm. Under normal physiologic conditions, an ECG has a characteristic pattern of waves corresponding to the electrical activity, contraction and relaxation of each heart chamber. This normal functioning is referred to as sinus rhythm and occurs at a heart rate of between 60 and 100 beats per minute at regular intervals.

As seen in the figure below, the various waves of an ECG tracing corresponding to the events of a single heartbeat are named with the letters P, Q, R, S and T. The interval between the P wave and the R wave, known as the PR interval, is a measure of conduction over the AV node. A normal PR interval is 0.12-0.20 seconds.

ECG Tracing Graph – Event Single Heartbeat



Arrhythmias

A disruption in the heart's normal rhythm or conduction of electrical signals is called an arrhythmia. An arrhythmia can take the form of the heart beating too quickly, too slowly, or with an irregular pattern. A faster than normal heart rate is a tachycardia; a slower than normal heart rate is a bradycardia. Symptoms of an arrhythmia can include palpitations, lightheadedness or dizziness, chest pain, shortness of breath, or sweating; these symptoms can be markedly severe, and in

advanced cases of some arrhythmias, resultant signs can include worse morbidities and even mortality. PSVT and atrial fibrillation are two of the most commonly occurring arrhythmias. While PSVT is characterized by a faster than normal heart rate where the heart beats at regular intervals, with AFib-RVR the heart often beats faster than normal and with an irregularly irregular rhythm. Pharmacologic treatment of PSVT focuses on terminating the arrhythmia using an agent to prolong the refractoriness (the recovery time between consecutive activations) of the AV node or to prolong conduction over the AV node. With AFib-RVR, there are two approaches to treatment: rate control to reduce the heart rate and rhythm control to restore sinus rhythm and prevent AFib recurrences.

Etripamil

We designed the molecule of etripamil and is developing the drug, a novel, potent and rapid-onset calcium channel blocker, as a nasal spray to be administered by the patient to terminate episodes of transient cardiovascular conditions as they occur. Rapid pharmacological action is both appropriate and sufficient to resolve an episode of SVT. We have completed Phase 3 development for PSVT. We are also developing etripamil to provide acute ventricular rate control for patients with symptomatic episodes of atrial fibrillation with rapid ventricular rate and are exploring other therapeutic applications in which a patient-administered, rapid-onset, non-dihydropyridine calcium channel blocking agent could provide patient benefit.

In our work to develop potential therapies, we sought to create new chemical entities as analogs of known molecular classes with clinically validated mechanisms of action. Our goal was to preserve the beneficial pharmacology of existing molecules while altering their pharmacokinetic profile with focused medicinal chemistry to produce drugs that are fast acting. As a result, we created a series of novel non-dihydropyridine, L-type calcium channel blockers containing chemical ester moieties that preserved the desired pharmacology on the heart but that could be rapidly metabolized in the blood by serum esterases. Etripamil resulted from this effort as a new chemical entity with a fast pharmacodynamic effect in humans, relative to oral calcium channel blockers.

We believe that the following attributes of etripamil make it a better treatment candidate for certain episodic cardiovascular conditions than current standards of care:

- Action: Etripamil is designed to be rapidly metabolized by blood-borne esterases, with the goal of reducing long-term side effects that may occur with chronic drug therapy.

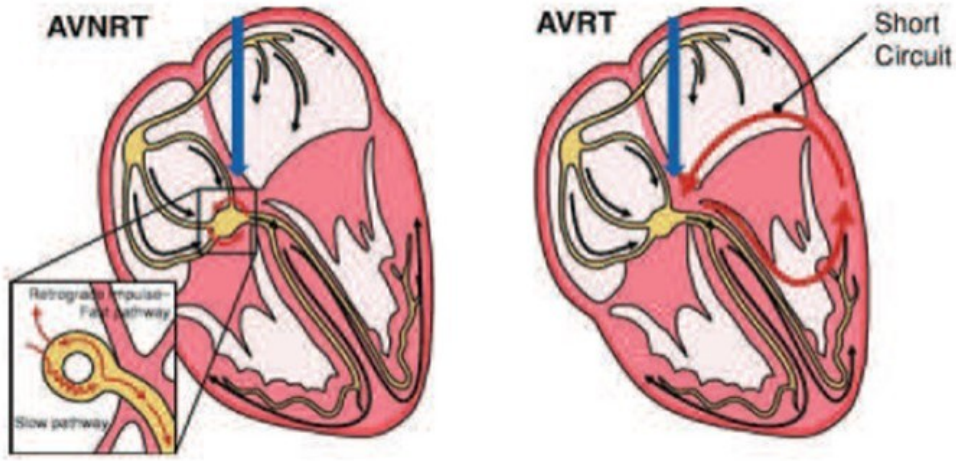
- Absorption: Etripamil is designed to be absorbed into the bloodstream in less than 10 minutes through the inner lining of the nose, yielding a rapid-onset pharmacologic pattern consistent with parenterally administered drugs.

- Administration: Etripamil is designed, and has been investigated, to empower patients to self-administer treatment outside of a medical setting and as prompted by a patient's symptoms.

PSVT

PSVT is a serious, markedly symptomatic, and recurring cardiac arrhythmia, which is caused by altered electrical conduction within the heart, involving the AV node and over an abnormal electrical circuit in the substantial majority of cases. In the most common form of PSVT, AV nodal reentrant tachycardia, or AVNRT, there is an abnormal limb of

electrical circuitry within the AV node which represents the substrate of the tachycardia. This abnormal circuitry is the basis for a reentrant arrhythmia which results in excessively rapid beating of both the atria and ventricles.



In the next most common form of PSVT, atrioventricular reciprocating tachycardia, or AVRT, there is an abnormal limb of electrical tissue, or bypass tract, that directly connects the atria and the ventricles. In AVRT, the bypass tract allows the signal to travel between the atria and ventricles as a "short circuit." AVRT involves the AV node, in addition to the bypass tract. Thus, for both AVNRT and AVRT – two PSVT types that require the AV node as a part of their abnormal circuit, or AV-nodal dependent PSVTs – a drug which targets the AV node can represent a potential treatment. Non-dihydropyridine calcium channel blockers are a class of drugs that target the AV node, reflecting why etripamil has been an excellent therapeutic candidate for AVNRT and AVRT termination.

Current Treatment Options for PSVT

Treatment for PSVT depends on the frequency, duration, and severity of the episodes as well as patient preference. Current options for patients with PSVT to terminate an episode of SVT include vagal maneuvers, IV medication or external shock delivered in the emergency department. Additionally, some practitioners prescribe oral medications, such as calcium channel blockers, beta blockers and antiarrhythmic drugs to be taken at the onset of an episode. However, these oral medications interventions are generally not acutely effective. Long-term strategies include chronic drug therapy to reduce the frequency of episodes and cardiac ablation to potentially cure the disease. Patients may also elect to not treat their symptoms and simply endure episodes of SVT when they occur.

Vagal maneuvers are commonly attempted to terminate an episode, with low to modest success rates. These are physiological maneuvers that stimulate the vagus nerve, which can terminate an SVT episode. These include gagging, massaging one carotid artery, holding one's breath and bearing down (Valsalva maneuver), immersing one's face in ice-cold water, or coughing.

Currently approved acute pharmacological therapy for the treatment of an acute episode of SVT includes IV administration of approved AV nodal-blocking agents in an acute care setting. The current standard of care for treatment of episodes of SVT is adenosine, but prior to its approval in 1990, episodes of SVT were treated with IV calcium channel blockers, such as verapamil or diltiazem. When given as a rapid IV bolus, adenosine blocks conduction over the AV node, thereby interrupting the arrhythmia circuit and restoring the heart back to sinus rhythm. Adenosine temporarily stops the heart and patients have reported experiencing chest tightness, flushing and a sense of impending death. Physicians report that patients tell them that they feel like they are going to die. Adenosine is eliminated from the body in less than one minute but cannot be self-administered as it requires IV access. In-hospital IV administrations are associated with higher healthcare costs and are also unsettling and inconvenient for the patient. IV calcium channel blockers also slow conduction over the AV node during the course of several minutes. However, they are associated with the risk of excessive slowing of the heart rate and

low blood pressure. According to treatment guidelines, patients in the acute care setting who fail pharmacologic treatment for PSVT could then receive direct current cardioversion, where an electric shock is applied to the heart to return it to sinus rhythm.

In an attempt to prophylactically control the frequency and duration of future SVT episodes, many patients will take chronic daily oral medications that modulate AV nodal conduction, such as beta blockers, L-type non-dihydropyridine calcium channel blockers, or antiarrhythmic drugs. Despite chronic daily oral medication, breakthrough SVT episodes that require visits to the emergency department may still occur, albeit for some patients at a reduced frequency. Chronic medication can lead to side effects such as sexual dysfunction or fatigue in the case of beta blockers and constipation in the case of verapamil. Some patients discontinue chronic oral medication due to intolerable side effects. Based on our market research, we estimate that approximately two thirds of patients with PSVT have been prescribed chronic medications such as beta blockers or calcium channel blockers to prevent SVT episodes or to treat other concomitant conditions such as hypertension.

The only potentially curative treatment available at the present time for PSVT is ablation, an invasive procedure, which works by directly cauterizing or freezing the short circuit that is the cause of the abnormal rhythm. This is achieved in an electrophysiology lab via catheters that are run through the patient's groin vessels and into the heart and uses burning or freezing techniques to destroy the heart's abnormal electrical tissue. Ablation single-procedure success rates for PSVT are reported to be 91% to 96%. However, we estimate that less than 10% of patients with PSVT per year choose this option, which we believe is due primarily to anxiety related to the procedure. Although ablations are generally considered to be safe by the treating community, as with any invasive procedure there are potential complications, which include bleeding, blood clots, pericardial tamponade, and transient or permanent heart block, with the latter requiring permanent pacemaker implantation.

Market Opportunity – Paroxysmal Supraventricular Tachycardia (PSVT)

We believe that PSVT is a large and under-recognized market that we estimate affects approximately two million Americans and results in over 600,000 healthcare claims in the United States alone per year, including more than 150,000 emergency department visits and hospital admissions and up to 80,000 ablations. Furthermore, we estimate that approximately 300,000 people are diagnosed with PSVT each year in the United States. We derive these estimates from the analysis of longitudinal claims data, which we believe is the most accurate method available to estimate the epidemiology of PSVT. A study in the Journal of Clinical Electrophysiology published in 2021 concluded that excluding patients with comorbid Atrial Fibrillation or Atrial Flutter, or AFib/AFL, leads to a conservative estimate of PSVT treated prevalence in the U.S. of approximately 1.3 million, while including those with comorbid AFib/AFL suggests a U.S. treated prevalence of approximately 2.1 million, with approximately 190,000 to 310,000 corresponding new cases each year.

Other published sources that attempt to quantify the epidemiology of PSVT, such as the MESA study published in the Journal of the American College of Cardiology in 1998, and the PREEMPT study published in the Journal of the American Heart Association in 2018, provide important demographic and clinical characteristic data on patients with PSVT. For example, in the MESA study, fewer than 40% of the adjudicated incident cases of PSVT would have been detected had the investigators limited their screening to those patients identified by the PSVT ICD9 Code (427.0). In addition, 21% of the incident patients with PSVT in the MESA study also had a diagnosis of atrial fibrillation (18%) or atrial flutter (6%). As an epidemiology tool, however, we believe these studies underestimate the incidence and prevalence of PSVT due to the episodic nature of the disease as well as the variability in the duration of the episodes, as the investigators in both studies relied only on data from patients presenting to healthcare settings acutely, with the episode confirmed on ECG during the encounter, to estimate the incidence and prevalence of PSVT.

Current treatment for PSVT also consumes significant healthcare resources. Research published in the American Journal of Cardiology in 2020 shows that costs for patients rose significantly in the pre-diagnosis year due to the difficulty of obtaining an accurate diagnosis. In the year following diagnosis, costs triple for those less than 65 years of age and double for those over 65 years of age, compared to matched controls. Total healthcare expenditures in the year following PSVT diagnosis ranged from $20,000 to $30,000 per patient, significantly higher than the expenditures observed for patients without PSVT (approximately $6,500 per patient). Significant increases for both age groups were noted for emergency department visits. For those less than 65, the average cost of hospitalizations doubled as their inpatient rates quadrupled. Of note, catheter ablations following diagnosis represent only 23% of this increased spend, meaning most costs are unrelated to ablations. In total, approximately $3 billion is spent annually in the U.S. on the management of PSVT.

Our Clinical Development Program for the Treatment of Paroxysmal Supraventricular Tachycardia

Current treatments do not address the medical need for a rapidly acting, effective, safe and patient-administered treatment that can be taken outside of a hospital or acute care setting at the onset of an SVT episode to restore the heart back to sinus rhythm. We believe that etripamil will fill this unmet need. We completed a Phase 1 clinical trial, which supported the selection of four doses of etripamil for Phase 2 development, followed by a Phase 2 clinical trial in adult patients to evaluate the effects of four doses in patients with PSVT. Both trials assessed nasally administered etripamil compared to placebo. Based on discussions with the FDA, we initiated a major Phase 3 clinical trial (NODE-301) in July, 2018 to assess the efficacy and safety of etripamil in the at-home setting and released topline data in March, 2020. We have completed a second pivotal Phase 3 trial (RAPID) which demonstrated highly statistically significant efficacy to convert PSVT and favorable safety/tolerability of the drug We have completed additional Phase 1 clinical trials, one that further characterized the PK and PD of intranasal etripamil in Japanese and non-Japanese healthy volunteers; a second that further characterized pharmacokinetics and safety of administering the drug in single- vs. repeated-dose approaches. We have also completed an open label Phase 3 safety trial (NODE-302), which provided further drug access to patients that had previously participated in the NODE-301 trial. The primary objective of the NODE-302 trial is to assess the safety of etripamil 70 mg in patients over multiple episodes. We completed a third Phase 1 clinical trial, assessing the impact of a repeat-dose regimen, in which patients take a second 70 mg dose of etripamil 10 minutes after a first dose of 70 mg, on the PK and safety of etripamil. We have completed NODE-303, which is an open label Phase 3 study that has the objective of collecting further safety data. The FDA has agreed that our Phase 3 clinical program could support an NDA filing in the United States.

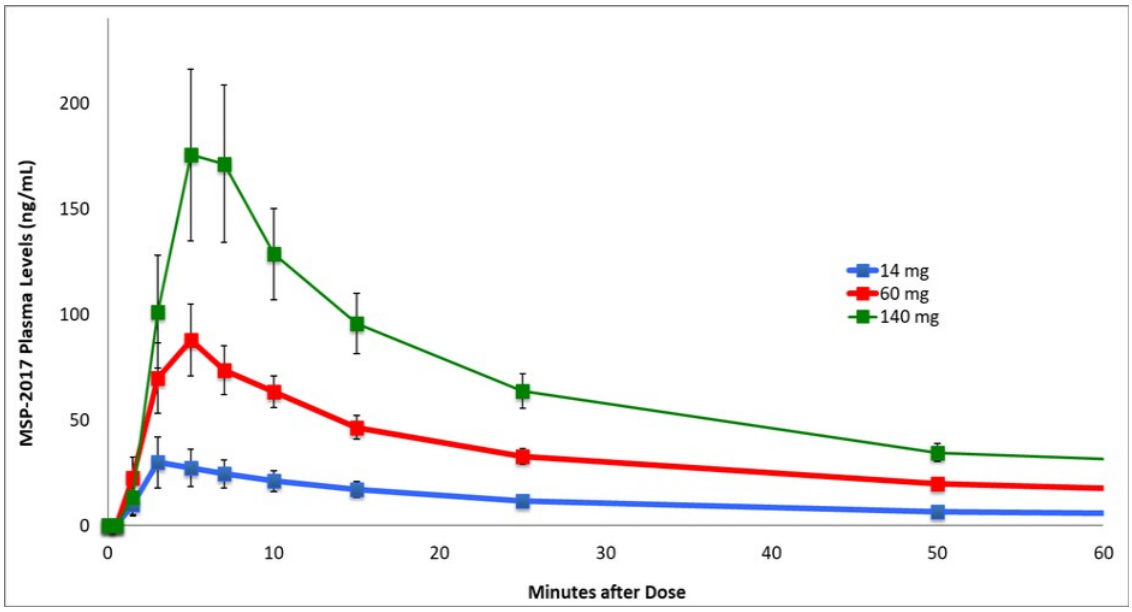
Phase 1 Clinical Data

We completed a Phase 1 clinical trial (MSP-2017-1096), in healthy volunteers, which was designed to assess the safety, PK profile, and cardiac pharmacology of intranasally administered etripamil in a randomized, double-blind, placebo controlled, single ascending dose trial. The trial's primary objective was to determine the maximum tolerated dose or maximum feasible dose of two different formulations of etripamil administered via the nasal route in healthy, adult male subjects. All doses of etripamil were generally well tolerated, and there was no difference in the safety profile and PK between the two formulations of etripamil, referred to as MSP2017A and MSP2017B. The most commonly reported side effects were localized to the administration site, e.g., nasal irritation and nasal congestion. Potential concerns such as syncope, pre-syncope, lightheadedness, or decreases in systolic blood pressure below 90 mmHg or AV nodal blocks of second degree or worse were not observed. The study of formulation MSP2017A was stopped at 60 mg and MSP2017B was further studied at higher doses (105 mg and 140 mg). The Phase 1 results supported the selection of four doses of etripamil for Phase 2 development. We are using these Phase 1 data, and resultant Phase 2 data, to support further clinical development of etripamil in two indications: PSVT and AFib-RVR.

PK analyses have demonstrated rapid absorption and elimination following nasal administration of etripamil, as well as dose proportional systemic exposure, or area under the curve, and maximum plasma concentration for etripamil and its primary inactive metabolite. These findings were consistent across a range of seven doses of drug tested up to 140 mg. The 140 mg dose was the maximal feasible dose because neither the concentration (350 mg/mL) nor the volume (200 µL) of solution administered in each nostril could be increased. Due to these characteristics of formulation and delivery, a maximum tolerated dose of etripamil was not established. The figure below shows the rapid absorption via the nasal route and the rapid decrease in plasma concentration of etripamil.

Phase 1: (MSP-2017-1096)

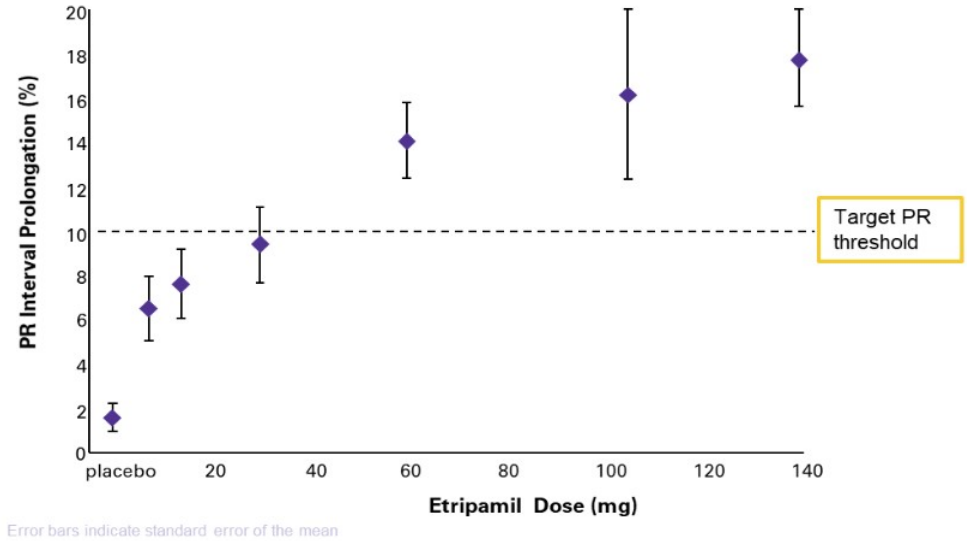
Pharmacokinetic Profile of Etripamil Plasma Concentrations



Error bars indicate standard error of the mean

Prolongation of the PR interval as measured by ECGs, which reflects the impact of drug on AV-nodal conduction, was utilized as the pharmacodynamic, or PD, measure. A linear relationship was observed between the dose of etripamil and prolongation of the PR interval. The 60 mg, 105 mg, and 140 mg doses demonstrated a 10% or greater PR prolongation, which is shown in the figure below. This correlates with the reported slowing of conduction over the AV node that is necessary to convert an SVT episode to sinus rhythm. Such slowing of AV-nodal conduction, reflected by PR interval prolongation, has been observed clinically and investigationally with known intravenous AV-nodal targeted agents such as verapamil, adenosine, and tecadenoson.

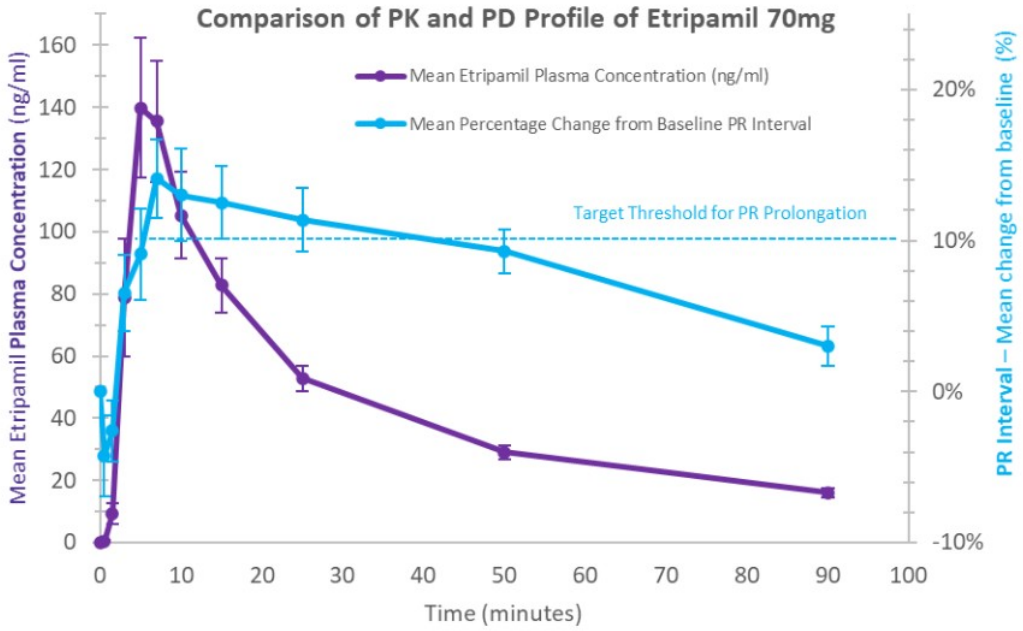
Phase 1: (MSP-2017-1096) - Pharmacology



We completed a second Phase 1 trial, NODE-102, comparing the PK and PD of etripamil 35 mg, 70 mg, and 105 mg versus placebo in Japanese and non-Japanese healthy volunteers. Once we determined there was no difference in PK and PD of etripamil between Japanese and non-Japanese participants, we pooled the data from the overall populations into a single dataset. We believe this trial provides further justification for the selected 70 mg dose in our Phase 3 program broadly, and may be used to support further clinical development of etripamil in Japan.

As shown in the figure below, we observed a correlation between the PK profile of etripamil 70 mg, measured by change in PR interval from baseline over time, and the plasma concentrations of etripamil. With regard to pharmacodynamics, an approximate 10% increase in the PR interval has been reported to be a marker of meaningful prolongation in AV-nodal conduction that is needed to terminate an episode of PSVT. The data as demonstrated on the blue line on the graph below indicates that etripamil 70 mg is potentially impacting AV nodal conduction at meaningful levels for a period up to approximately 50 minutes.

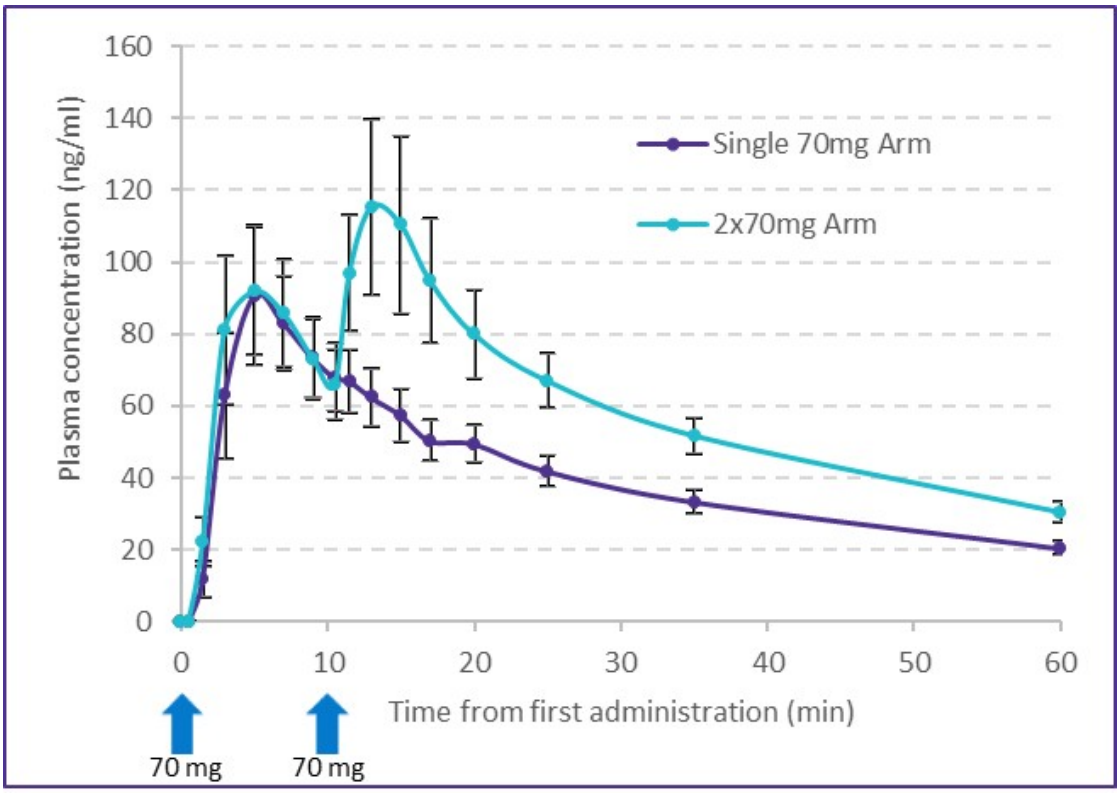
Phase 1: (MSP-2017-1205) NODE-102



The Phase 3 RAPID study incorporated a repeat-dose administration regimen of study drug (70 mg of etripamil or placebo). Specifically, patients were instructed to administer a repeat administration of study drug if they did not experience relief from symptoms of PSVT within 10 minutes of the first administration of study drug. This tailored, staged drug regimen utilizes a repeat-dose similar to current PSVT treatment practices with intravenous drugs in the emergency department setting. Pharmacologic data supporting a repeat-dose approach were obtained from a Phase 1 study. A repeat dose regimen (two doses of 70 mg etripamil administered 10 minutes apart) was tested in study NODE-103. As shown in the figure below, this regimen resulted in greater systemic exposure to etripamil, as measured by an apparently increased second maximum concentration after the second administration, as well as an elevated total Area Under the Curve, compared to single-dose administration of 70 mg. Furthermore, from visual inspection of the data, the intended two-bolus PK plot can be observed.

We believe these PK data supports the hypothesis underlying our RAPID trial regimen that a second administration will augment etripamil exposure, while maintaining safety, and will improve impact of the drug on AV-nodal conduction thereby resulting in a greater therapeutic effect.

Phase 1: (NODE-103). One dose of 70-mg etripamil vs. repeat dose regimen administered 10 minutes apart



Error bars = standard error

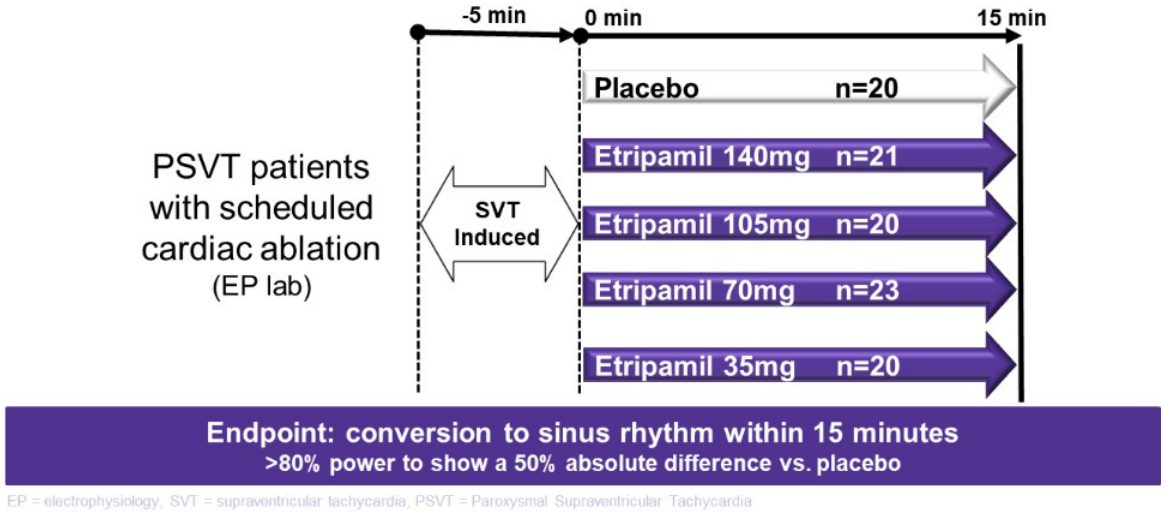
Phase 2 Clinical Data

We completed a Phase 2 multicenter, randomized, double-blind, placebo controlled clinical trial in the United States and Canada, NODE-1, to evaluate the effects of four doses of etripamil in patients with PSVT. In order to demonstrate the effectiveness and safety of etripamil to terminate SVT in a controlled setting, we conducted the study in the electrophysiology, or EP, laboratory setting, where an SVT episode could be induced in patients scheduled to undergo an EP study and ablation. The primary objective of this trial was to demonstrate the superiority of at least one dose of etripamil over placebo in terminating SVT. The secondary objectives were to determine the minimally effective dose of etripamil, to establish a dose related efficacy trend for etripamil, and to evaluate the safety of etripamil in a clinical setting. The trial was statistically powered at more than 80% to show a 50% absolute difference of etripamil versus placebo.

The trial enrolled 199 patients, of which 95 withdrew prior to dosing: 70 due to inability to induce (n=42) or to sustain (n=28) SVT, five based on physician discretion, one lost to follow up, one due to withdrawal of consent, and 18 for other reasons. The mean age of patients was 52.2 years (range, 19 to 85 years). As shown in the figure below, SVT was induced and sustained for five minutes in 104 patients, who were randomized into one of five dosing cohorts. Four cohorts received intranasal doses of etripamil (35 mg, 70 mg, 105 mg, or 140 mg) and one cohort received matching placebo. All doses of study drug were delivered in a double-blind fashion in which healthcare providers administered four 100 µL sprays from four different single-spray devices. There were no imbalances in baseline characteristics across the five treatment groups.

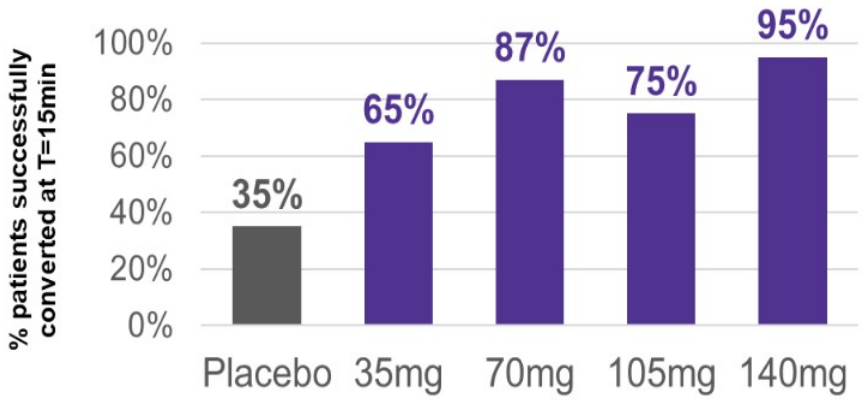
The mean heart rate in SVT at time = 0 was 177 bpm in the placebo group and 168 bpm, 173 bpm, 180 bpm, and 155 bpm in the etripamil 35-mg, 70-mg, 105-mg and 140-mg groups, respectively.

Phase 2: (MSP-2017-1109) NODE 1 – Clinical Trial Design



The primary endpoint in this clinical trial was the conversion of SVT to sinus rhythm within 15 minutes after administration of etripamil or placebo. As shown in the figure below, the percentage of patients in whom SVT converted to sinus rhythm within 15 minutes of study drug administration was 65% with 35 mg etripamil, 87% with 70 mg, 75% with 105 mg and 95% with 140 mg, compared with 35% in the placebo arm. The three highest doses of etripamil showed statistically significant conversion rates compared with placebo. Statistical significance expresses the probability that the results of a particular study could have occurred purely by chance. Statistical significance is assessed by the FDA and other health regulatory agencies in evaluating marketing approval applications. FDA and other regulatory agencies review the strength of the statistical evidence and whether it supports the claims of the applicant. The primary endpoint, statistical methods for the trial and a p-value boundary for achieving statistical significance for a clinical trial are typically defined before the trial begins. If the probability of observing the calculated statistic is smaller than the p-value boundary, the primary endpoint is considered statistically significant. P-value is a conventional statistical method for measuring the statistical significance of clinical results. A p-value of 0.05 or less represents statistical significance, meaning there is a less than 1in 20 likelihood that the observed results occurred by chance. The FDA utilizes statistical significance, as measured by p-value, as an evidentiary standard of efficacy and typically requires a p-value of 0.05 or less to demonstrate statistical significance.

Phase 2: (MSP-2017-1109) NODE 1 - Etripamil Conversion Rates from SVT to Sinus Rhythm

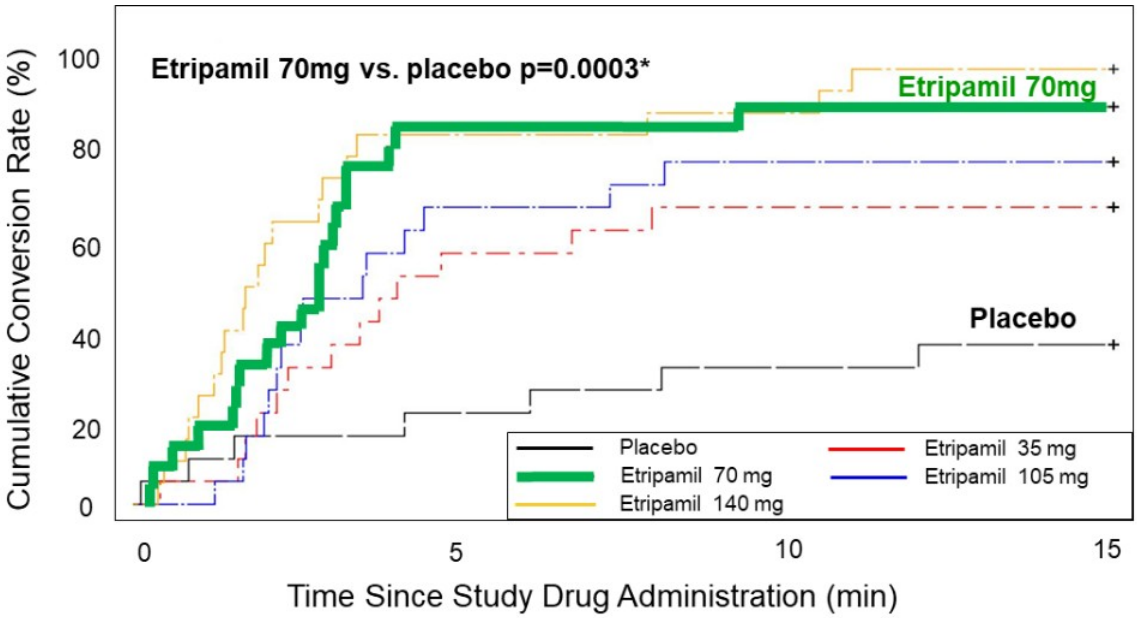


# patients converted at 15 min	7/20	13/20	20/23	15/20	20/21
p-value		0.1128	0.0006	0.0248	<.0001

Source: Stambler, B.S. et al.; Etripamil Nasal Spray for Rapid Conversion of Supraventricular Tachycardia to Sinus Rhythm; J Am Coll Cardiol. 2018;72(5):489–97

In a post-hoc analysis conducted to inform our Phase 3 trial design, the patients' times to conversion of SVT to sinus rhythm were examined. As shown in the following Kaplan Meier plot, patients successfully converting to sinus rhythm during the 15-minute study window, the three highest doses of etripamil (140 mg, 105 mg, and 70 mg) demonstrated statistically significant shorter time to conversion of SVT compared with placebo. The 70-mg dose showed a rapid onset of action with a median time to conversion of less than three minutes after nasal administration of etripamil. Doses of drug above 70 mg, given as single-dose administrations in this study, did not yield meaningfully greater degrees of conversion of SVT. These data contributed greatly to selection of etripamil dose for the Phase 3 program.

Phase 2: (MSP-2017-1109) NODE 1 – Etripamil Time to Conversion from Supraventricular Tachycardia to Sinus Rhythm



*Hazard Ratio and 95% Confidence Intervals etripamil 70mg vs. placebo; 4.99 (2.09, 11.93)

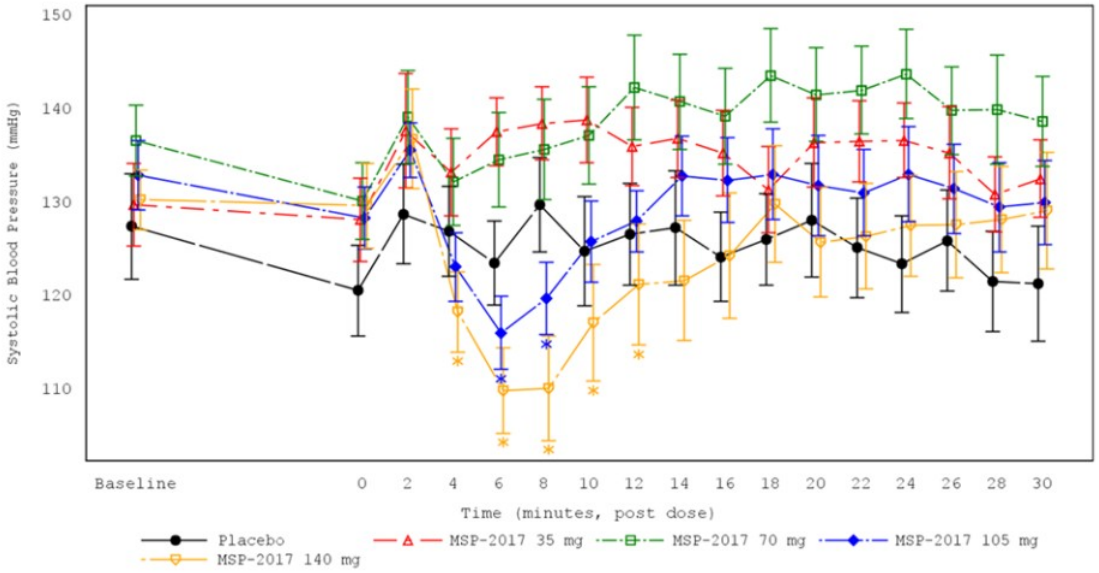
Overall, etripamil was well tolerated, and the most common adverse events were localized to the nasal route of administration, e.g., nasal irritation or nasal congestion, reported by up to 60% and 45% of patients, respectively, after etripamil (versus none after placebo). Specifically, the 70-mg dose was reported to have 48% nasal irritation and 26% nasal congestion; however, these were transient and required no specific intervention. Most adverse events were mild (44.2%) or moderate (24.0%) across all treatment groups. At least one adverse event considered related to the study drug, according to the investigator assessment, was reported in 17 (85.0%) patients in the etripamil 35-mg group, 18 (78.3%) in the 70-mg group, 15 (75.0%) in the 105-mg group, 20 (95.2%) in the 140-mg group and 4 (20.0%) in the placebo group. The incidence of adverse events was not dose-dependent. Hypotension, or low blood pressure, was reported as an adverse event in two patients, one in the 105-mg group and one in the 140-mg group. Neither event led to sequelae or a serious classification.

A total of three patients experienced severe adverse events that were considered possibly related to etripamil. One patient who received a 35-mg dose of etripamil experienced facial flushing, shortness of breath, and chest discomfort. One patient who received a 105-mg dose of etripamil had nausea and vomiting, as well as a severe and serious cough. One patient who received a 140-mg dose of etripamil experienced a severe adverse event of second-degree AV block with relative hypotension, beginning five minutes after conversion to sinus rhythm; the AV block resolved after 43 minutes, was without sequelae observed, and ablation was subsequently performed. There were no adverse events that led to study discontinuation or death.

Calcium channel blockers have the potential to cause hypotension as a side effect. Thus, in our Phase 2 clinical trial, we recorded vital signs, including heart rate and blood pressure, before induction of SVT and every two minutes for 30 minutes after study drug was given (see figure below). We observed no meaningful reduction in mean blood pressure in the 35 mg or 70 mg etripamil cohorts but observed a transient decrease in the mean blood pressure in the two highest cohorts, 105 mg, and 140 mg. Due to the induction of SVT, the mean systolic blood pressure decreased at time 0 compared to the average at 20 and 10 minutes before SVT induction. Compared to baseline and time 0, systolic blood pressure

measurements recorded from two minutes to 16 minutes post study drug administration showed no decrease in mean systolic blood pressure in the placebo or 35-mg groups, and maximum mean decreases of 2 mm Hg four minutes post dose in the 70-mg group, 17 mm Hg six minutes post dose in the 105-mg group, and 20 mm Hg six minutes and eight minutes post dose in the 140-mg group. As illustrated in the figure below, mean blood pressure reductions in these two groups were transient.

Phase 2: (MSP-2017-1109) NODE 1 – Etripamil Systolic Blood Pressure Over Time



* $p < 0.05$ vs baseline.

Baseline is defined as the average of the -20 and -10 minutes pre-dose measurements. Time 0 is defined as the average of the measurements during SVT between -5 and 0 minutes before study drug administration. Mean and standard error (SEs) values were calculated based on available data at the relevant time point. MSP-2017 means etripamil. Error bars indicate standard error of the mean.

Based on the combination of efficacy and safety data from our Phase 2 trial, we selected the 70 mg dose of etripamil for our subsequent clinical trials.

Clinical Development of Etripamil for a PSVT Indication

In accordance with on our interactions with regulatory agencies, our Phase 3 clinical program has included:

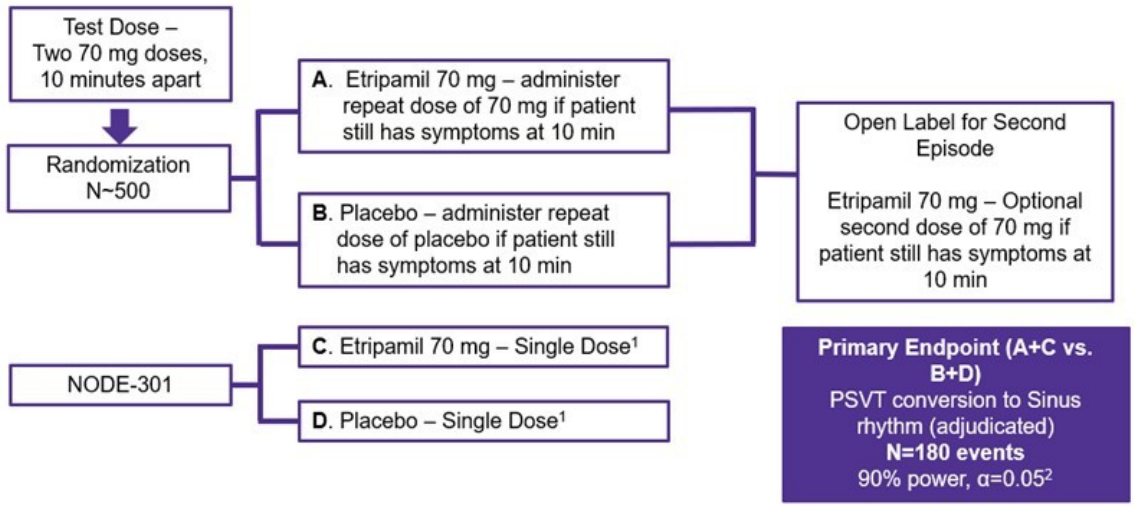
- RAPID, a confirmatory pivotal efficacy trial to assess the time to conversion of PSVT to sinus rhythm due to treatment with etripamil compared to placebo in the at-home setting and, in this trial, utilizing an optional repeat-dose regimen.
- NODE-301 part 1, a pivotal efficacy trial to assess the time to conversion of PSVT to sinus rhythm due to treatment with etripamil compared to placebo in the at-home setting.
- NODE-302, an open-label extension of NODE-301 that enrolled patients who completed NODE-301 in order to collect safety data on subsequent (recurrent) episodes in the at-home setting, and.

- NODE-303, an open-label global safety trial to complete the safety assessment of etripamil in the at-home setting to support an NDA and other regulatory filings.

Phase 3 Clinical Trials

RAPID Study. The RAPID trial was a placebo-controlled, double-blinded, randomized, event-driven Phase 3 clinical trial conducted in the United States, Canada, and Europe to evaluate 70 mg of etripamil (with an optional repeat dose of drug) versus placebo in terminating an SVT episode in the at-home setting. RAPID, also named NODE-301 part 2, was originally intended to collect double-blind data from randomized patients who had not yet experienced an SVT event after the NODE-301 study reached its target number of adjudicated SVT events. After receiving guidance from the FDA on our Phase 3 program, we amended and expanded NODE-301 part 2 and renamed it the RAPID trial; and, with regulatory agreement, RAPID is inferentially separate from NODE-301 part 1. The RAPID trial, an event-driven trial like the prior Phase 3 one, was projected to enroll approximately 500 patients and was defined to be completed after a total of 180 confirmed SVT events occurred. Patients enrolled in the RAPID trial were randomized 1:1 (etripamil:placebo). The graphic below shows the design of the RAPID trial. The protocol amendment changing NODE-301 part 2 to RAPID, and incorporating an important repeat-dose treatment regimen, was implemented across all clinical study sites over 2021. Prior to the RAPID / repeat-dose amendment being fully implemented, a total of 34 patients dosed themselves with single dose study drug of which 29 were confirmed by the adjudication committee to be SVT (i.e., groups C+D in the trial design graphic, which had been randomized 2:1, etripamil:placebo).

Phase 3: (MSP-2017-1138) RAPID – Trial Design



(1) Arms C and D (single-dose regimen) will be only the patients enrolled under NODE-301 who have had an episode prior to the RAPID Study protocol amendment
(2) Wilcoxon analysis modeling from NODE-301 data

Under the RAPID statistical analysis plan (SAP), the primary efficacy endpoint for the study was defined as time to conversion over the first 30 minutes, with a target p-value of less than 0.05. (This endpoint was agreed upon with FDA and other regulatory bodies because it, when assessed in either a prespecified or in a post hoc analysis for NODE-301 part 1, was statistically significant and showed a compelling treatment effect.) This endpoint supports the desire and need of patients to address their PSVT symptoms rapidly during an episode and have a normal cardiac rhythm restored during a time-window that would avoid additional medical intervention and visiting an emergency department. Based on interactions with PSVT-treating physicians and cardiovascular thought leaders, it is clear that a 50% conversion rate within 60 minutes would be a clinically meaningful outcome given the highly symptomatic nature of SVT episodes and the lack

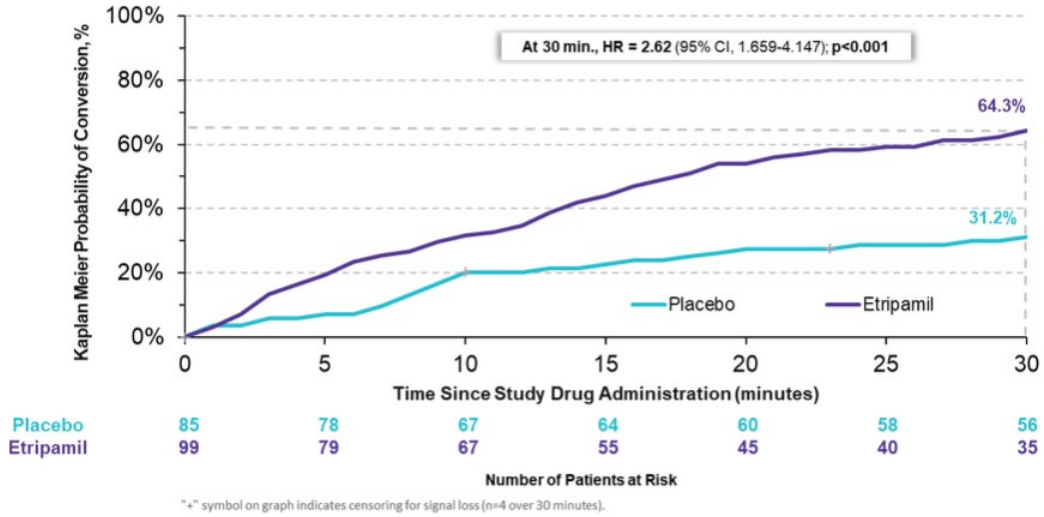
of approved at-home treatments. In addition to its clinical relevance, primary assessment by 30 minutes is a time aligned with the drug's known pharmacologic characteristics.

The design of the RAPID study was based on power calculations utilizing NODE-301 Part-1 study data. The Kaplan–Meier probabilities of conversion to sinus rhythm by 30 minutes as 54% under etripamil treatment and 35% under placebo were the basis for effect-size assumptions, and indicated that 180 patients, each with a PSVT event confirmed by adjudication, would provide 90% power to detect a 19% relative-reduction treatment difference for the primary endpoint at a 2-sided-significance level of 0·05. It was anticipated that ≥500 patients would be randomized to accrue requisite confirmed PSVT events. Later and earlier time point data from NODE-301 part 1 for time to conversion, for patient reported outcomes, and for emergency department utilization were used to define assessments for secondary analyses in RAPID; these secondary analyses were pre-planned to fully characterize the efficacy profile of etripamil.

RAPID was performed at approximately 160 study sites in North America and Europe and enrolled patients with similar inclusion and exclusion criteria as the prior randomized Phase 3 study. Key eligibility criteria included, similar to the prior Phase 3 study: patients were aged ≥18 years with electrocardiogram-documented history of PSVT with sustained, symptomatic episodes (≥20 minutes). In the RAPID study, as prompted by PSVT symptoms, patients self-administered a first 70-mg etripamil or placebo dose and, if symptoms persisted beyond 10 minutes, a repeat dose of study drug (70-mg etripamil or placebo). Continuously recorded electrocardiographic data were blindly adjudicated for the primary endpoint, time-to-conversion of PSVT to sinus rhythm for ≥30 seconds by 30 minutes of first dose. Pre-defined secondary endpoints assessed the robustness of the primary findings and measured use of additional medical interventions and emergency department use for episodes of PSVT. Safety outcomes were assessed. This trial was registered at www.clinicaltrials.gov (NCT03464019).

Among the 692 patients randomized, 184 self-administered the study drug for confirmed PSVT. Kaplan–Meier estimates of conversion rates by 30 minutes were 64.3% with etripamil and 31.2% with placebo (hazard ratio=2.62; P<0.001), and statistically significant differences were observed by 300 minutes as well (hazard ratio=1.70; P<0.001). Median time-to-conversion was 17.2 minutes (etripamil) versus 53.5 minutes (placebo). The Kaplan–Meier plot of cumulative incidence of conversion by 30 minutes is in the below figure.

Primary Endpoint: Conversion of Adjudicated PSVT to NSR 30 min



There were reduced rates of additional medical interventions and emergency-department visits following etripamil administration compared to placebo in the RAPID study, and these rates are consistent with those observed in NODE-301 part-1. Neither trial was sized to detect significantly different rates between treatment groups in need of additional acute care. Thus, a predefined analysis was performed on a data-set pooled between RAPID and NODE-301 part-1, confirming alignment between the studies' findings, and showing reduced rates of additional medical interventions (25.4% under placebo versus 14.6% under etripamil [P=0.013]) and emergency-department visits (22.4% under placebo versus 13.6% under etripamil [P=0.035]). Risk-reductions observed in RAPID indicate that the number-needed-to-treat with etripamil to convert an episode of PSVT within 30 minutes of drug administration is 3.0 and to prevent an emergency visit for PSVT is 14.1, within the range for effectiveness of a treatment for a symptomatic condition.

The majority of adverse events were localized at the administration site and mild; there were no serious etripamil-related events. A blinded examination of ECG data showed no instances of AV block or significant pauses during randomized drug administration or in the hours following that.

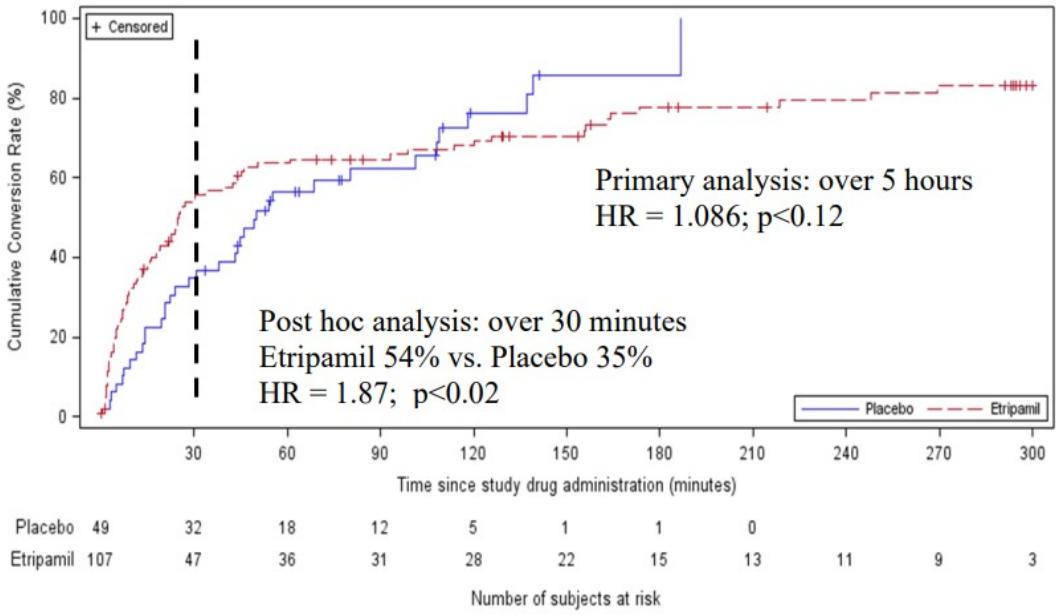
Results from the RAPID trial demonstrate that intranasal etripamil, self-administered in an at-home setting, with initial- and repeat-dosing prompted by symptoms, was superior to placebo for rapid PSVT conversion and well-tolerated. This symptom-prompted treatment approach was further supported by findings of improvement in patient-defined symptoms of PSVT. Reduced rates of additional medical interventions and emergency-department visits observed with etripamil potentially support this drug regimen for lessening the healthcare burden of PSVT.

NODE-301. NODE-301 is a placebo-controlled, double-blinded, randomized, event-driven Phase 3 clinical trial conducted in the United States and Canada to evaluate 70 mg of etripamil versus placebo in terminating an SVT episode in the at-home setting. As shown in the figure below, the primary endpoint is the time to conversion over a five-hour monitoring period following the administration of the study drug. Prior to randomization, eligible patients administered a test dose of 70 mg of etripamil in the investigator's office while in sinus rhythm in order to assess tolerability. Patients successfully completing the test dose were randomly assigned to the etripamil or placebo cohorts (2:1 randomization) and sent home with the study drug and a small portable electrocardiographic cardiac monitor to be used during patients' subsequent SVT episodes. Upon experiencing symptoms of an SVT episode, patients were instructed to first apply the

cardiac monitoring device to record ECG data, then attempt a vagal maneuver, and, if that was not successful in terminating the episode, to then administer the study drug. Patients' ECG data were recorded using the electrocardiographic cardiac monitoring device for a period of five hours after study drug administration. Patients returned to the clinic for a follow up visit within one week following their SVT event for collection of further information. NODE-301 enrolled 431 patients across 65 sites in the United States and Canada, with 156 patients (107 etripamil, 49 placebo) receiving etripamil for an adjudicated true PSVT episode.

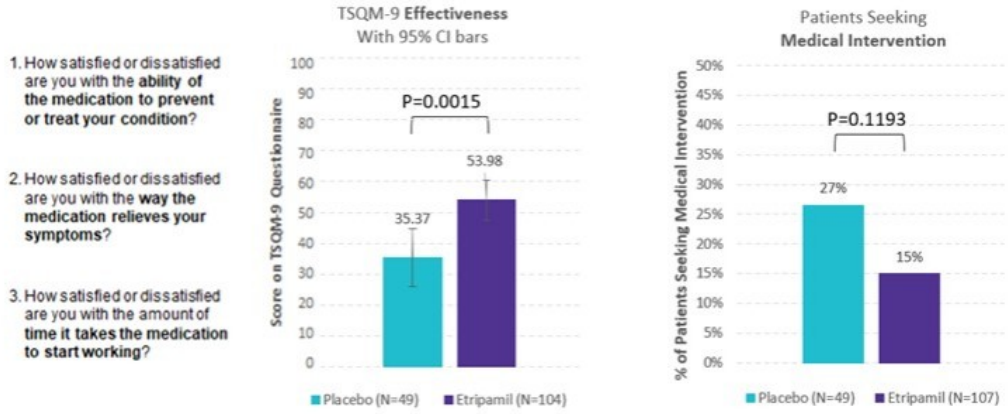
In March 2020, we reported topline results of the NODE-301 trial, referred to as NODE-301 part 1. The first part of NODE-301 did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five-hour period following study drug administration, however, prespecified and post hoc assessments at 30 minutes were significant. The median time to conversion for etripamil was 25 minutes (95% CI: 16, 43) compared to 50 minutes (95% CI: 31,101) for placebo. As shown in the top figure below, despite the activity of etripamil to convert PSVT and its separation from placebo in the first approximately 30 to 60 minutes following study drug administration, results from the latter part of the analysis confounded the statistical analysis of the primary endpoint. Analysis of the first 30 minutes of the Kaplan Meier curve, shown in the bottom graph below, and the post hoc results at that time point were a 54% rate of conversion for the etripamil patients and 35% for the placebo patients. The results were statistically significant with a hazard ratio of 1.87 and a p-value of 0.02. Prespecified landmark analyses were aligned with these post hoc findings and also significant.

Phase 3: (MSP-2017-1138) NODE-301 Part 1 Efficacy – Time to Conversion over 5 Hours (Primary analysis) and Time to Conversion over 30 minutes (post hoc analysis, aligned with prespecified analyses at 30 minutes)



The study also demonstrated statistically significant improvements in patients taking etripamil compared to those taking placebo in the secondary endpoint of patient reported treatment satisfaction, as measured by a treatment satisfaction questionnaire for medication (TSQM-9), including global satisfaction (p=0.0069) and effectiveness scores (p=0.0015). Additionally, there was a trend towards improvement in the percentage of patients seeking rescue medical intervention, including in the emergency department, with 15% and 27% etripamil and placebo patients, respectively, reporting such intervention (p=0.12).

Phase 3: (MSP-2017-1138) NODE-301 Key Secondary Efficacy Endpoints



Overall, etripamil was well tolerated when self-administered as a test dose during sinus rhythm or as a post-randomization dose during symptomatic PSVT. The most common (≥5%) adverse events occurring within 24 hours of a test dose or those occurring more frequently with etripamil within 24 hours of a randomized dose were nasal discomfort, nasal congestion, epistaxis, rhinorrhea, throat irritation, and increased lacrimation, all of which were related to the nasal route of administration. The incidence of all other adverse events, including those related to abnormal vital signs, laboratory results, and ECG findings, was balanced between the 2 groups. No serious adverse events were observed within 24 hours of taking study drug.

NODE-302. NODE-302 is the open label extension trial of NODE-301. We designed NODE-302 to primarily evaluate the safety of etripamil when self-administered without medical supervision and to monitor the safety and efficacy of etripamil for the treatment of multiple episodes of SVT.

Patients who had successfully dosed with the study drug in NODE-301 and completed a study closure visit were eligible to enroll in NODE-302 to manage any subsequent episodes of SVT. Eligibility was also contingent on satisfying all inclusion and exclusion criteria, including not experiencing a serious adverse event related to the study drug or the study procedure that precludes the self-administration of etripamil.

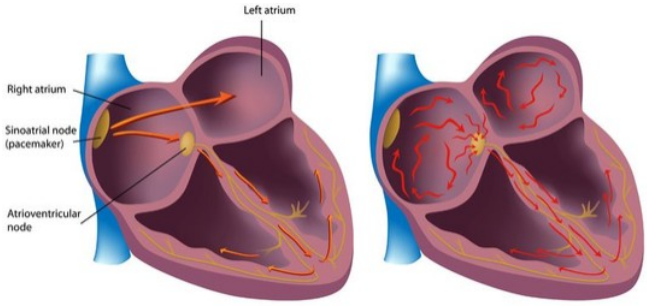
We initiated NODE-302 in December, 2018. The trial completed enrollment in 2020 and the study was presented at the Heart Rhythm Society Scientific Sessions as a late-breaking clinical trial in May, 2022, and is in the process of being published. Overall, the safety and tolerability profile of etripamil 70 mg was favorable and generally consistent with what was observed in the NODE-301 study including for patients experiencing recurrent episodes.

NODE-303. NODE-303 is an open-label global safety trial enrolling patients who did not participate in NODE-301, NODE-302, or RAPID in order to collect safety data that, when combined with the safety data from the rest of the program, will form the safety dataset to be evaluated by the FDA and other regulatory agencies, forming the basis for marketing approval. We designed NODE-303 to evaluate the safety of etripamil when self-administered as prompted by symptoms and without medical supervision, and to evaluate the safety and efficacy of etripamil over multiple episodes of SVT. The NODE-303 trial is designed to closely reflect the expected utilization of etripamil in the post approval or 'real-world'

setting and, for example, does not include an in-office safety test dose and includes a broad patient population including patients taking concomitant beta blockers and calcium channel blockers. In this study, patients have the opportunity to manage up to four episodes of SVT. NODE-303 was initiated in October 2019 utilizing the single 70 mg etripamil administration. In 2021, following FDA's agreement, we initiated the change from the single 70 mg etripamil administration to the 70 mg repeat-dose treatment regimen. The FDA's acceptance was based on initial safety data of the repeat-dose regimen experience gained in the RAPID study and the overall safety data from the etripamil clinical program.

Atrial Fibrillation

Atrial fibrillation (AFib) is a common arrhythmia with an irregular and often rapid heart rate that can increase the risk of stroke, heart failure, and other heart-related complications. AFib can be, and often is, highly symptomatic. Symptoms include heart palpitations, shortness of breath, fatigue, and weakness, and underlying cardiac disorders can be worsened. Episodes of atrial fibrillation can come and go, or patients may have AFib that does not resolve. Although the heart arrhythmia in AFib itself usually is not life-threatening, it is a serious medical condition that sometimes requires emergency treatment. Additionally, AFib is associated with elevated risk of embolism and stroke and anticoagulant medications, also called blood thinners, are commonly prescribed to manage this risk. Uncertainty around symptom timing and episode length may impact a patient's quality of life. During AFib, the heart's two upper chambers, the atria, beat chaotically and irregularly—out of coordination with the two lower chambers, the ventricles, of the heart, as shown in the figure below.



Classification of AFib is used to determine the appropriate treatment modality for patients. The American Heart Association, or AHA, and the American College of Cardiology, or ACC, categorize AFib patients based on disease progression. These categories are defined as follows: paroxysmal, which involves AFib episodes that resolve spontaneously within seven days of symptom onset; persistent, which involves AFib episodes that fail to terminate within seven days of symptom onset and require treatment to convert back to sinus rhythm; long-standing persistent, which involves atrial fibrillation episodes that last longer than one year despite continued attempts to restore sinus rhythm; and permanent, which involves a joint decision by the treating provider and patient to no longer pursue cardioversion and leave the patient in AFib, focusing on rate control and symptom management. Disease progression in AFib is common with approximately 40% of AFib patients in the paroxysmal stage, 30% of AFib patients in the persistent and long-standing persistent stage, and 30% of AFib patients in the permanent stage. For purposes of simplicity, we do not differentiate the long-standing persistent classification from the persistent classification as the clinical impact of this differentiation has not been characterized. Concomitant structural heart irregularities including valvular dysfunction and the presence of active symptoms may also help to characterize patients and influence treatment decisions.

A common complication of atrial fibrillation is a rapid ventricular rate which can be defined as a heart rate of ≥110 beats per minute. Rapid, irregular, and inefficient cardiac pumping function induced by a rapid ventricular rate accounts for hemodynamic instability and many of the arrhythmia's symptoms. Frequently, new-onset patients with atrial fibrillation present with symptoms related to rapid ventricular rate.

Current Treatment Options for Atrial Fibrillation with Rapid Ventricular Rate

There are currently two major approaches to managing atrial fibrillation: rate control to lower a rapid heart rate, and rhythm control to restore and maintain a regular (sinus) rhythm and to prevent recurrent atrial fibrillation. Either of these management approaches, often performed by pharmacological means, may be given chronically or acutely, depending on patient preference and episode frequency and severity. The decision to pursue rate and/or rhythm control for atrial fibrillation episodes is dependent on a variety of factors, including episode severity, episode frequency, patient preference, and safety and tolerability of treatments. Several rhythm control strategies exist, including electrical cardioversion, catheter-based cardiac ablation, and anti-arrhythmic drug therapy. For rate control, the rapid heart rate of atrial fibrillation is typically treated with AV nodal blocking drugs (for example, calcium channel blockers, beta blockers, or less commonly digoxin) to control symptoms and improve cardiac function/hemodynamic stability. Oral rate control drugs used acutely do not provide immediate ventricular rate control due to a 30-to-60-minute delayed onset of action. Breakthrough episodes of symptomatic atrial fibrillation often require urgent medical treatment with IV calcium channel blockers and beta-blockers under medical supervision, usually in the emergency department to quickly reduce heart rate before transitioning a patient back to oral therapy.

The “pill-in-pocket” anti-arrhythmic strategy is described by the AHA and ACC guidelines as the utilization of an oral dose of flecainide or propafenone as an attempt to restore sinus rhythm shortly after the onset of symptomatic atrial fibrillation. Neither drug referenced in the guideline is approved by any regulatory agency for the use outlined in the guideline. Pill-in-pocket rhythm control strategies are considered by physicians for patients who demonstrate favorable outcomes to these medications in the clinic and who are thought to be reliable enough to administer them appropriately. Initial administration of pill-in-pocket medication is recommended in a monitorable setting due to potential AV node dysfunction or a proarrhythmic response and may be preceded by beta-blocker or calcium channel blocker therapy if the patient is not chronically rate controlled.

Rate controlling agents (for example, calcium channel blockers and beta blockers) may also be administered acutely on an as needed (or PRN) basis. Though the AHA and ACC guidelines do not explicitly acknowledge this approach, participants in market research conducted by us indicate a significant share of patients are managed this way. PRN rate control is more prominently used in paroxysmal patients who do not tolerate chronic medications but experience symptomatic, infrequent atrial fibrillation episodes. Our patient market research from 2018 estimated that approximately 40% of patients use an additional rate control medication to manage acute symptoms of atrial fibrillation. Additionally, our physician market research commissioned in 2021 suggests that both clinical/interventional cardiologists and electrophysiologists prescribe PRN rate control for some of their paroxysmal and persistent patients.

Market Opportunity – Atrial Fibrillation with Rapid Ventricular Rate

The American Heart Association estimates that in 2016 approximately five million people suffered from AFib in the United States. This estimate is projected to increase over the next ten years; the AHA suggests a prevalence of seven million by 2030, while the Centers for Disease Control (CDC) reports this prevalence as increasing to 12 million over the same time period, representing an approximately 6% annual growth rate. From market research with treating physicians, we estimate that approximately 40% of these patients have paroxysmal AFib, 30% have persistent AFib, and 30% have permanent AFib. Acute episodes of symptomatic AFib are often treated with the approaches described above. However, due to the concerning nature of AFib symptoms, patients often present to the emergency department. In the ED, patients are treated with IV calcium channel blockers or beta-blockers to quickly reduce heart rate and/or anti-arrhythmic or electrical cardioversion before transitioning a patient back to oral therapy. According to the Healthcare and Utilization Project, 660,000 patient visits to the emergency department in 2016 were attributed to AFib (ICD-10 diagnosis codes I48.0, I48.1, I48.2, I48.91). Additionally, approximately 465,000 patients were admitted to the hospital with AFib (same ICD-10 codes).Our qualitative and quantitative market research indicates that the target addressable market for etripamil in patients with AFib-RVR is approximately 30-40% of the diagnosed population of patients with atrial fibrillation. We derive this percentage estimate from 2021 market research studies conducted by us that involved qualitative interviews and quantitative surveys with a total of 275 electrophysiologists, general cardiologists, and interventional cardiologists. The physicians in the two studies were asked to estimate the share of patients experiencing ≥1 symptomatic episode of AFib-RVR requiring treatment per year. In response, physicians in the quantitative survey reported approximately 40% of paroxysmal patients, 40% of persistent patients, and 30% of permanent patients met this classification. This research

suggests the share of patients experiencing ≥1 symptomatic episode of AFib requiring treatment may constitute 30-40% of the prevalent atrial fibrillation population on a weighted average basis.

We believe that etripamil has the potential to be developed such that it can be used by patients to rapidly reduce their heart rate in the at-home setting to provide a supplemental option to the acute oral rate or rhythm control strategy their physician would use. When presented with a target product profile reflecting this potential use case, approximately two thirds of the physicians in the 2021 market research study perceived utility in the product profile, which could serve as a "bridge" to the onset of acute oral agents. According to physicians, it can take hours for patients to feel an alleviation of symptoms using acute oral rate and rhythm control. During this time, patients may experience concerning symptoms that often prompt them to seek emergent care. We believe that the combination of convenient delivery, potency, rapid onset and short duration of action of etripamil has the potential to move the current treatment setting for some acute episodes of AFib out of the burdensome and costly emergency department.

Current atrial fibrillation management consumes significant healthcare resources in the United States. The American Heart Association published a report in 2016 summarizing the current and projected cost burden of cardiovascular diseases in the United States. This report suggests atrial fibrillation resulted in $25 billion in direct medical costs in 2016 (approximately 7% of all cardiovascular diseases) and another $7 billion in indirect costs (i.e., $32 billion in total costs). Additionally, the forecasted growth in atrial fibrillation prevalence is anticipated to result in healthcare expenditures of $46 billion in direct costs and $10 billion in indirect costs in the United States by 2030.

Clinical Development Plan for Atrial Fibrillation with Rapid Ventricular Rate

The Phase 2, double-blind, placebo-controlled, proof-of-concept study, Reduction of Ventricular Rate in Patients with Atrial Fibrillation (ReVeRA), in patients with atrial fibrillation with rapid ventricular response (AFib-RVR), is being conducted in Canada and the Netherlands in collaboration with the Montreal Heart Institute, the WCN network, and other research centers. We began enrollment in ReVeRA in the first quarter of 2021 to evaluate the potential effectiveness of etripamil to reduce ventricular rate in patients with atrial fibrillation and rapid ventricular rate. The ReVeRA Phase 2 double blind, placebo controlled, proof-of-concept trial is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect. The trial is to be conducted in the hospital or emergency department setting under medical supervision. The expansion of study sites in Canada and the program most recently having sites in the Netherlands is anticipated to promote enrollment. These trial data, along with data from the PSVT program, is expected to form the basis for proceeding with a full, registrational program in AFib-RVR.

Etripamil in Other Therapeutic Applications

Our goal in expanding our pipeline around etripamil is to apply the same paradigm-changing aspiration that we have for supraventricular tachycardias like PSVT and AFib-RVR to other cardiac and potentially non-cardiac conditions where we believe that a rapid-onset dihydropyridine L-type calcium channel blocker could potentially deliver significant clinical and quality of life benefits for patients. We believe that the insights that led to the development of etripamil for the treatment of PSVT are relevant in other indications where AV-nodal blocking agents with blood vessel widening activity have demonstrated clinical utility. Both calcium channel blockers and beta blockers are commonly used to manage not only supraventricular tachycardias like PSVT or AFib-RVR, and other conditions.

Sales and Marketing

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. If etripamil receives marketing approval, we plan to commercialize it in the United States leveraging industry trends regarding staged deployment of resources, digital/omnichannel investments, and a focused, specialty sales force that could consist of our own employees, outsourced sales professionals, or a hybrid model using both internal and external resources. We believe that this commercial organization at the launch of etripamil will consist of a field force of <100 individuals calling on primarily clinical cardiologists who treat large populations of patients with PSVT, supported by strategic

investments in digital and targeted non-personal promotion. As we establish reimbursement for etripamil with commercial and Medicare payers, we anticipate that this investment in omnichannel promotion will grow, targeting both prescribers and patients. Aligned to this expansion, our field force could grow to 150 to 200 field sales representatives calling on top-prescribing clinical cardiologists, interventional cardiologists, electrophysiologists, and high-volume primary care physicians who have a history of prescribing cardiovascular therapies. We believe an organization of this size would allow us to reach prescribers that collectively care for a substantial portion of patients diagnosed with PSVT in the United States. Given the importance of increasing awareness and educating patients with PSVT, we also anticipate deploying focused direct-to-patient marketing campaigns for etripamil. We anticipate that our sales force could also support the commercialization of additional product candidates treating cardiovascular diseases. We would expect to conduct the initial buildout of our commercial organization following NDA submission for etripamil. At this time, we may pursue and believe that we can maximize the value of etripamil by retaining commercialization rights in the United States and entering into collaboration agreements for certain territories outside the United States, including the European Union.

Manufacturing

We currently rely on third party contract manufacturing organizations, or CMOs, for all of our required raw materials, nasal spray device, active pharmaceutical ingredient, or API, and finished product for our clinical trials and for our preclinical research. We require all of our CMOs to conduct manufacturing activities in compliance with current good manufacturing practice, or cGMP, requirements. We have assembled a team of experienced employees and consultants to provide the necessary technical, quality and regulatory oversight over our CMOs and have implemented a comprehensive plan for audits of our CMOs. Currently, we have development contracts and quality agreements with our CMOs for the manufacturing of etripamil drug substance and drug product. We currently have enough manufactured supply of etripamil to complete our ongoing registration trials. We also may elect to pursue additional CMOs for manufacturing supplies of regulatory starting materials in the future and for the filling of the nasal spray device, labeling, packaging, storage and distribution of investigational drug products. We plan to continue to rely on third party manufacturers for any future trials and commercialization of etripamil, if approved. We anticipate that these CMOs will have capacity to support commercial scale production, but we do not have any formal agreements at this time with these CMOs to cover commercial production. If etripamil is approved by any regulatory agency, we intend to enter into agreements with a third-party contract manufacturer and one or more backup manufacturers for the commercial production of etripamil.

Competition

Drug development is highly competitive and subject to rapid and significant technological advancements. Our ability to compete will significantly depend upon our ability to complete necessary clinical trials and regulatory approval processes, and effectively market any drug that we may successfully develop. Our current and potential future competitors include pharmaceutical and biotechnology companies, academic institutions and government agencies. The primary competitive factors that will affect the commercial success of etripamil or any other product candidate for which we may receive marketing approval include differentiation any competitor’s product regarding efficacy, safety, tolerability, dosing convenience, price, coverage and reimbursement. Many of our potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, as well as in obtaining regulatory approvals and commercializing those product candidates in the United States and in foreign countries. It is also possible that a competitor may develop a cure or more effective treatment method for the diseases we are targeting, which could render our current or future product candidates non-competitive or obsolete, or reduce the demand for our product candidates before we can recover our development and commercialization expenses.

We are not aware of any approved drug or any drug candidate in clinical development for a patient with PSVT to self-administer treatment to terminate SVT episodes. In the acute setting, IV treatments of generic drugs such as adenosine, verapamil and diltiazem, are routinely given. Additionally, some practitioners prescribe oral medications, such as calcium channel blockers, beta blockers and antiarrhythmics to be taken at the onset of an episode. However, these interventions are not acutely effective and are not approved by the FDA or other regulatory agencies for this use.

For atrial fibrillation, there are a number of marketed generic antiarrhythmic drugs that are used for chronic and/or acute rate control, such as metoprolol, propranolol, esmolol, pindolol, atenolol, nadolol, verapamil and diltiazem. We are aware of several drugs or new formulations of existing drugs under development or recently under development for atrial fibrillation, including InRhythm (flecainide), a sodium channel blocker in Phase 3 from InCarda Therapeutics, Inc., and Gencaro (bucindolol hydrochloride), a beta blocker in Phase 2 from ARCA biopharma, Inc.

Intellectual Property

We have filed numerous patent applications pertaining to etripamil and possible future product candidates, formulations containing etripamil, methods of making such formulations and clinical use. We strive to protect and enhance the proprietary technology, invention and improvements that are commercially important to the development of our business by seeking, maintaining, and defending our intellectual property. We also rely on know-how, continuing technological innovation and potential in-licensing opportunities to develop, strengthen and maintain our position in the field of cardiac arrhythmias, such as PSVT, and immediate rate control in atrial fibrillation, as well as other medical conditions affecting the cardiovascular system. Additionally, we intend to rely on regulatory protection afforded through data exclusivity and market exclusivity, as well as patent term extensions, where available.

As of February 28, 2023, our patent portfolio as it pertains to etripamil included:

- a patent family containing six U.S. patents, projected to expire in 2028, a pending U.S. patent application, which, if granted, is projected to expire in 2028, as well as corresponding patents in Australia, Brazil, Canada, China, Europe, Hong Kong, India, Japan, Mexico, New Zealand and South Korea, directed to etripamil, pharmaceutical compositions including etripamil, and uses of etripamil such as to treat cardiac arrhythmias, including PSVT and atrial fibrillation; and

- a patent family containing one U.S. patent, projected to expire in 2036, a pending U.S. patent application, which, if granted, is projected to expire in 2036, as well as corresponding patents in Australia, China, Europe, Hong Kong, Israel, Japan, Mexico, Russia, South Africa, and Ukraine and corresponding patent applications in Brazil, Canada, China, Europe, Hong Kong, India, New Zealand, South Africa, and South Korea, directed to formulations including etripamil, methods of making such formulations, and uses of such formulations to treat cardiac arrhythmias, such as PSVT and atrial fibrillation.

- a patent family containing pending applications in the United States, Canada, and Europe, which, if granted, is projected to expire in 2041, directed to uses of formulations including etripamil to treat cardiac arrhythmias, such as PSVT and atrial fibrillation, or migraines.

The terms of individual patents may vary based on the countries in which they are obtained. Generally, patents issued for applications filed in the United States are effective for 20 years from the earliest effective non-provisional filing date in the absence, for example, of a terminal disclaimer shortening the term of the patent or patent term adjustment increasing the term of the patent. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a results of FDA regulatory review periods. The restoration period cannot be longer than five years and the total term, including the restoration period, must not exceed 14 years following FDA approval. The duration of patents outside the United States varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest non-provisional filing date.

In addition to patents and patent applications that we own, we rely on know-how to develop and maintain our competitive position. We seek to protect our proprietary technology and processes, and obtain and maintain ownership of certain technologies, in part, through confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners.

Our future commercial success depends, in part, on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; and operate without infringing valid enforceable patents and proprietary rights of third parties. Our ability to

stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents that cover these activities. With respect to our owned intellectual property, we cannot be sure that patents will issue from any of the pending patent applications which we own or from any patent applications that we may file in the future, nor can we be sure that any patents that may be issued in the future to us will be commercially useful in protecting etripamil or any future product candidates and methods of using or manufacturing the same. Moreover, we may be unable to obtain patent protection for certain aspects of etripamil or future product candidates generally, as well as with respect to certain indications. See the section entitled "Risk Factors—Risks Related to Our Intellectual Property" for a more comprehensive description of risks related to our intellectual property

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local levels, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products, such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the drug development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve a pending New Drug Application, or NDA, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well controlled clinical trials, in accordance with good clinical practice, or GCP, requirements to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of an NDA;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- satisfactory completion of an FDA inspection of selected clinical sites to assure compliance with GCPs and the integrity of the clinical data;

- payment of user fees; and
- FDA review and approval of the NDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some nonclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold.

In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well controlled clinical trials to generate enough data to statistically evaluate the safety and efficacy of the product for approval, to establish the overall risk benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted, at least annually, to the FDA, and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements, or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User

Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act, certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP requirements.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and takes several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including

Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications, manufacturing changes or other labeling claims, are subject to further testing requirements and prior FDA review and approval. There also are continuing annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as application fees for supplemental applications with clinical data.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or

- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label, although physicians, based on their independent medical judgement, may prescribe approved drugs for unapproved indications. However, biopharmaceutical companies may share truthful and not misleading information that is otherwise consistent with the labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting their promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws may impact, among other things, our current and future business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain the business or financial arrangements and relationships with healthcare providers and other parties through which we market, sell and distribute our products for which we obtain marketing approval. These laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations, including, without limitation, those laws described below.

The federal Anti-Kickback Statute prohibits any person or entity from, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties laws.

Federal civil and criminal false claims laws, including the federal civil False Claims Act, which can be enforced by individuals through civil whistleblower and qui tam actions, and civil monetary penalties laws, prohibits any person or entity from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their respective implementing regulations, impose specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities, which include certain healthcare providers, healthcare clearinghouse and health plans, that create, receive, maintain or transmit individually identifiable health information in connection with providing a service for or on behalf of a covered entity, and their covered subcontractors. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members.

We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, state laws that require drug manufacturers to report information on the pricing of certain drugs, and state and local laws that require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of available statutory exceptions and regulatory safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to significant criminal, civil and administrative penalties including damages, fines, imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, implementation of corporate compliance programs, reporting of payments or transfers of value to healthcare professionals, and additional data privacy and security requirements.

Coverage and Reimbursement

The future commercial success of our, or any of our collaborators', product candidates, if approved, will depend in part on the extent to which third-party payors, such as governmental payor programs at the federal and state levels, including

Medicare and Medicaid, private health insurers and other third-party payors, provide coverage of and establish adequate reimbursement levels for our product candidates. Third-party payors generally decide which products they will pay for and establish reimbursement levels for those products. In particular, in the United States, no uniform policy for coverage and reimbursement exists. Private health insurers and other third-party payors often provide coverage and reimbursement for products based on the level at which the government, through the Medicare program, provides coverage and reimbursement for such products, but also have their own methods and approval process apart from Medicare determinations. Therefore, coverage and reimbursement can differ significantly from payor to payor.

In the United States, the European Union, or EU, and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of products, particularly for new and innovative products, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third-party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for products. For example, federal and state governments reimburse products at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of products. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of products, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party payor reimbursement may not be available to enable us to realize an appropriate return on our investment in product development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our product candidates, if approved, or exclusion of our product candidates from coverage and reimbursement. The cost containment measures that third-party payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates.

Healthcare Reform

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidates profitably, if approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded health care programs, and increased governmental control of drug pricing.

There have been several U.S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates.

The PPACA became law in March 2010 and substantially changed the way healthcare is financed by both third-party payors. Among other measures that may have an impact on our business, the PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare

Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, the PPACA extends manufacturers' Medicaid rebate liability, expands eligibility criteria for Medicaid programs, and expands entities eligible for discounts under the Public Health Service Act.

There have been executive, judicial and Congressional challenges to certain aspects of the PPACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the PPACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the PPACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." On June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Further, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in PPACA marketplaces through plan year 2025. The IRA also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. It is possible that the PPACA will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration will impact the PPACA.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. In August 2011, the President signed into law the Budget Control Act of 2011, as amended, which, among other things, included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which began in 2013 and, following passage of subsequent legislation, will continue until 2031 unless additional Congressional action is taken. Under current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. In January 2013, the American Taxpayer Relief Act of 2012 was enacted and, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Further, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. More recently, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, the Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. Further, the IRA, among other things (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. Additionally, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our product candidates. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a drug, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Employees and Human Capital

Patients inspire all we do. Milestone employees are passionate about creating a solution for patients who suffer from PSVT and other related illness as we work together on our mission to develop innovative cardiovascular medicines. We have built a culture of high performance based on our core values:

- *Patients First:* Everything we do is with the patient in mind. We listen to and partner with patients and place their well-being at the core of all our initiatives.
  Our patients inspire us.

- *Teamwork:* Milestone employees support, challenge and care for each other.
  Employees engage with one another through their teams, but also through our weekly gatherings, outings and friendly competitions and challenges.
  Collaboration is key.

- *Entrepreneurial Mindset:* Milestone places a high value on grit, courage and resolve. Milestone's organizational energy has the sense of a startup.
  Employees are encouraged to think like an owner.

- *Every Idea Matters:* Sometimes the best ideas evolve from where it is least expected.
  All ideas are welcome.

- *Humility, Empathy and Integrity:* We act individually and as a team with these three attributes in mind in all we do.
  We care to do what is right.

Our human capital objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards.

As of December 31, 2022, we had 39 full-time employees, 15 of whom were primarily engaged in research and development activities. Four of these employees have an M.D. or Ph.D. degree. None of our employees is represented by a labor union and we consider our employee relations to be excellent.

Facilities

Our headquarters is currently located in Montréal (Québec), Canada and consists of 7,700 square feet of leased office space under a lease that expires in November 2025 with an option to terminate in November 2023. We also have a U.S. subsidiary in Charlotte, North Carolina that occupies 13,050 square feet of leased office space under a lease that expires in September 2027.

Legal Proceedings

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceeding against us that we believe could have an adverse effect on our business, operating results or financial condition.

Corporate Information

Our principal executive offices are located at 1111 Dr. Frederik-Philips Blvd., Suite 420, Montréal, Québec, Canada H4M 2X6, and our telephone number is (514) 336-0444. Our US offices are located at 6210 Ardrey Kell Rd, Suite 650, Charlotte, NC 28277 and our telephone number is (704) 848-5316.

Available Information

We maintain an internet website at www.milestonepharma.com and make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act of 1934, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission ("SEC"). You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors," as a source of information about us.

The information on our website is not incorporated by reference into this Annual Report on Form 10-K and should not be considered to be a part of this Annual Report on Form 10-K. Our website address is included in this Annual Report on Form 10-K as an inactive technical reference only.

Investors and others should note that we announce material information to our investors using one or more of the following: SEC filings, press releases and our corporate website, including without limitation the "Investors" and "Events and Presentations" sections of our website. We use these channels, as well as social media channels such as LinkedIn, in order to achieve broad, non-exclusionary distribution of information to the public and for complying with our disclosure obligations under Regulation FD. It is possible that the information we post on our corporate website or other social media could be deemed to be material information. Therefore, we encourage investors, the media, and others interested in our company to review the information we post on the "Investors" and "Events and Presentations" sections of our corporate website and on our social media channels. The contents of our corporate website and social media channels are not, however, a part of this Annual Report.

ITEM 1A. RISK FACTORS

An investment in shares of our common shares involves a high degree of risk. You should carefully consider the following information about these risks, together with the other information appearing elsewhere in this Annual Report on Form 10-K, consolidated financial statements and related notes thereto and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding to invest in our common shares. The occurrence of any of the following risks could have a material adverse effect on our business, financial condition, results of operations and future growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. In these circumstances, the market price of our common shares could decline, and you may lose all or part of your investment. We cannot assure you that any of the events discussed below will not occur. Such risks may be amplified by the effects of the COVID-19 pandemic and its potential impact on our business and the global economy.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant operating losses since inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future and may never achieve or maintain profitability.

Since inception in 2003, we have incurred significant operating losses. Our net loss was $58.4 million and $42.9 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $266.3 million We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Since inception, we have devoted substantially all of our efforts to research and preclinical and clinical development of etripamil, as well as to expanding our management team and infrastructure. It could be several years, if ever, before we have a commercialized drug. We expect that our existing cash and cash equivalents, as well as funding provided by our Strategic Financing Agreement signed on March 27, 2023 that provides an immediate receipt of $50 million and an opportunity of another $75 million with the achievement of certain milestones, to be sufficient to fund our operations under our current operating plan.

The net losses we incur may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if, and as, we:

- continue our ongoing and planned development of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of PSVT and our ongoing Phase 2 clinical trial of etripamil for the treatment of atrial fibrillation and rapid ventricular rate, or AFib-RVR;
- seek marketing approvals for etripamil for the treatment of PSVT and other cardiovascular indications and any future product candidates that successfully complete clinical trials;
- establish a sales, marketing, manufacturing and distribution capability, either directly or indirectly with third parties, to commercialize etripamil or any future product candidate for which we may obtain marketing approval;
- build a portfolio of product candidates through development, or the acquisition or in-license of drugs, product candidates or technologies;
- initiate preclinical studies and clinical trials for etripamil for any additional indications we may pursue, and for any additional product candidates that we may pursue in the future;
- maintain, protect and expand our intellectual property portfolio;
- hire additional administrative, marketing, sales, clinical, regulatory and scientific personnel;

- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and

- incur additional legal, insurance related, accounting and other expenses associated with operating as a public company.

To become and remain profitable, we must succeed in developing and eventually commercializing drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing clinical trials of etripamil and any future product candidates that way may pursue, obtaining regulatory approval, procuring commercial-scale manufacturing, marketing and selling etripamil and any future products for which we may obtain regulatory approval, as well as discovering or acquiring and then developing additional product candidates. We are only in the preliminary stages of some of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

Because of the numerous risks and uncertainties associated with drug development, we are unable to accurately predict the timing or amount of expenses or when, or if, we will be able to achieve profitability.

Our expenses could increase beyond our expectations if we are required by the U.S. Food and Drug Administration, or FDA, the European Medicines Agency or other regulatory authorities to perform studies in addition to those we currently expect, or if there are any delays in the initiation and completion of our clinical trials or the development of etripamil or any future product candidates.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our common shares could also cause you to lose all or part of your investment.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage company founded in 2003, and our operations to date have been largely focused on raising capital, organizing, staffing our company and undertaking preclinical studies and conducting clinical trials for etripamil. As an organization, we have not yet demonstrated an ability to successfully complete clinical development, obtain regulatory approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successful clinical development and commercialization of products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Additionally, we expect our financial condition and operating results to continue to fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We will require substantial additional funding to finance our operations. If we are unable to raise capital when needed, we could be forced to delay, reduce or terminate our development of etripamil or other operations.

Based on our research and development plans, we expect that our existing cash and cash equivalents, as well as funding provided by our Strategic Financing Agreement signed on March 27, 2023 that provides an immediate receipt of $50 million and an opportunity of another $75 million with the achievement of certain milestones, will be sufficient to fund

our operations for at least the next 12 months. However, we will need to obtain substantial additional funding in connection with our continuing operations and planned activities. Our future capital requirements will depend on many factors, including:

- the timing, progress and results of our ongoing and planned clinical trials of etripamil in PSVT, AFib-RVR and in other indications;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of etripamil for additional indications or any future product candidates that we may pursue;
- our ability to establish collaborations on favorable terms, if at all;
- the ability of vendors who we rely on to accurately forecast expenses and deliver on expectations;
- the costs, timing and outcome of regulatory review of etripamil and any future product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for etripamil and any future product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of etripamil and any future product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the extent to which we acquire or in-license other product candidates and technologies; and
- the costs of operating as a public company.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. For example, we recently announced that the pivotal NODE-301 trial of etripamil for PSVT did not meet its primary endpoint. In addition, etripamil and any future product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all. We may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. In addition, we may not be able to access a portion of our existing cash, cash equivalents and investments due to market conditions. For example, on March 10, 2023, the Federal Deposit Insurance Corporation (FDIC) took control and was appointed receiver of Silicon Valley Bank. Similarly, on March 12, 2023, Signature Bank and Silvergate Capital Corp. were each swept into receivership. If other banks and financial institutions enter receivership or become insolvent in the future in response to financial conditions affecting the banking system and financial markets, our ability to access our existing cash, cash equivalents and investments may be threatened and could have a material adverse effect on our business and financial condition. Weakness and volatility in capital markets and the economy, in general or as a result of bank failures or macroeconomic conditions such as rising inflation, could limit our access to capital markets and increase our costs of borrowing. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or altogether terminate our research and development programs or future commercialization efforts.

Economic uncertainty, including related to inflation, may adversely affect our results of operations.

Our results of operations may be materially affected by global economic conditions, including inflation, which has recently increased at the fastest pace in nearly 40 years, sustained uncertainty regarding future economic conditions, prolonged tightening of credit markets and changes in tax rates. In recent years, the U.S. and other significant economic markets have experienced cyclical downturns, and worldwide economic conditions remain uncertain. While such uncertainty persists, investor concerns over inflation, market volatility, geopolitical tensions, COVID-19 variants and other such public health crises may cause deteriorating market conditions with adverse effects on our business, financial condition and operating results.

Raising additional capital may cause dilution to our shareholders, restrict our operations or require us to relinquish rights to our product candidates.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through public or private equity or debt financings, third-party funding, marketing and distribution arrangements, as well as other collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, such as the Convertible Notes (as defined herein), your ownership interest may be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a shareholder. Debt and equity financings, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as redeeming our shares, making investments, incurring additional debt, making capital expenditures, declaring dividends or placing limitations on our ability to acquire, sell or license intellectual property rights.

If we raise additional capital through future collaborations, strategic alliances or third-party licensing arrangements, we may have to relinquish valuable rights to our intellectual property, future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us. If we are unable to raise additional capital when needed, we may be required to delay, limit, reduce or terminate our drug development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise develop and market ourselves.

Our ability to use our non-capital loss carryforwards to offset future taxable income may be subject to certain limitations.

In general, where control of a corporation has been acquired by a person or group of persons, subsection 111(5) of the Income Tax Act (Canada), or the Canadian Tax Act, and equivalent provincial income tax legislation restrict the corporation's ability to carry forward non-capital losses from preceding taxation years. We have not performed a detailed analysis to determine whether an acquisition of control for the purposes of subsection 111(5) of the Canadian Tax Act has occurred after each of our previous issuances of common shares or preferred shares. In addition, if we undergo an acquisition of control, our ability to utilize non-capital losses could be limited by subsection 111(5) of the Canadian Tax Act. As of December 31, 2022, we had Canadian federal and provincial non-capital loss carry forwards of $184.3 million and $181.4 million, respectively, which expire beginning in 2026 through 2042. In addition, we also have scientific research and experimental development expenditures of $21.9 million and $26.5 million, respectively, for Canadian federal and provincial income tax purposes, which have not been deducted. These expenditures are available to reduce future taxable income and have an unlimited carry-forward period. Research and development tax credits and expenditures are subject to verification by the tax authorities, and, accordingly, these amounts may vary. Future changes in our share ownership, some of which are outside of our control, could result in an acquisition of control for the purposes of subsection 111(5) of the Canadian Tax Act. Furthermore, our ability to utilize non-capital losses (or U.S. equivalents) of companies that we may acquire in the future may be subject to limitations. As a result, even if we attain profitability, we may be unable to use a material portion of our non-capital losses and other tax attributes, which could negatively impact our future cash flows.

Our subsidiary's ability to use its U.S. net operating loss carryforwards and certain other tax attributes for U.S. income tax purposes may be limited.

As of December 31, 2022, we had U.S. federal net operating loss carryforwards, or NOLs, of $38.1 million as a result of expenses incurred by Milestone Pharmaceuticals USA, Inc., our wholly owned subsidiary. Under current U.S. federal tax law, NOLs incurred in taxable years ending beginning after December 31, 2017 may be carried forward indefinitely. However, the deductibility of such NOLs in taxable years beginning after December 31, 2022 is limited to 80% of taxable income. It is uncertain if and to what extent various states will conform to the federal law. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change (by value) in its equity ownership over a three year period, the corporation's ability to use its pre change NOL carryforwards and other pre change tax attributes (such as research tax credits) to offset its post change income may be limited. It is possible that we have experienced one or more ownership changes in the past. In addition, we may also experience ownership changes in the future as a result of subsequent shifts in our share ownership some of which may be outside of our control. As a result, if we earn net taxable income, our ability to use our pre ownership change NOL carryforwards to offset U.S. federal taxable income may be subject to limitations, which could potentially result in increased future tax liability to us. In addition, at the state level, there may be periods during which the use of NOLs is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

Risks Related to the Development of Our Product Candidates

We have only one product candidate, etripamil, for which we are currently pursuing clinical development. Our future success is substantially dependent on the successful clinical development and regulatory approval of etripamil. If we are not able to obtain required regulatory approvals for etripamil or any future product candidates, we will not be able to commercialize etripamil or any future product candidates and our ability to generate revenue will be adversely affected.

Etripamil is currently our only product candidate. We have not obtained regulatory approval for etripamil or any product candidate, and it is possible that neither etripamil nor any product candidates we may seek to develop in the future will ever obtain regulatory approval. Neither we nor any future collaborator is permitted to market any drug product candidates in the United States or other countries until we receive regulatory approval from the FDA or applicable foreign regulatory agency. The time required to obtain approval or other marketing authorizations by the FDA and comparable foreign

regulatory authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions.

Prior to obtaining approval to commercialize etripamil and any other drug product candidate in the United States or elsewhere, we must demonstrate with substantial evidence from well controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such product candidates are safe and effective for their intended uses. Results from nonclinical studies and clinical trials can be interpreted in different ways. Even if we believe the nonclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities. The FDA may also require us to conduct additional nonclinical studies, including human factor studies, or clinical trials for our product candidates either prior to or post-approval, or it may object to elements of our clinical development program. In addition, the FDA typically refers applications for novel drugs, like etripamil and potentially any future product candidates, to an advisory committee composed of outside experts. The FDA is not bound by the recommendation of the advisory committee, but it considers such recommendation when making its decision.

Of the large number of products in development, only a small percentage successfully complete the FDA or comparable foreign regulatory authorities' approval processes and are commercialized. The lengthy approval or marketing authorization process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval or marketing authorization to market etripamil or any future product candidates, which would significantly harm our business, financial condition, results of operations and prospects.

We have invested a significant portion of our time and financial resources in the development of etripamil. Our business is dependent on our ability to successfully complete development of, obtain regulatory approval for, and, if approved, successfully commercialize etripamil and any future product candidates in a timely manner.

Even if we eventually complete clinical testing and receive approval of a new drug application, or NDA, or foreign marketing application for etripamil and any future product candidates, the FDA or the comparable foreign regulatory authorities may grant approval or other marketing authorization contingent on the performance of costly additional clinical trials, including post-market clinical trials. The FDA or the comparable foreign regulatory authorities also may approve or authorize for marketing a product candidate for a more limited indication or patient population that we originally request, and the FDA or comparable foreign regulatory authorities may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a product candidate. Any delay in obtaining, or inability to obtain, applicable regulatory approval or other marketing authorization would delay or prevent commercialization of that product candidate and would materially adversely impact our business and prospects.

In addition, the FDA and comparable foreign regulatory authorities may change their policies, adopt additional regulations or revise existing regulations or take other actions, which may prevent or delay approval of our future products under development on a timely basis. Such policy or regulatory changes could impose additional requirements upon us that could delay our ability to obtain approvals, increase the costs of compliance or restrict our ability to maintain any marketing authorizations we may have obtained.

We may not be successful in our efforts to expand our pipeline of product candidates beyond etripamil for PSVT.

We intend to build a pipeline of product candidates beyond etripamil for PSVT and progress these product candidates through clinical development. For example, we recently began enrollment in a Phase 2 clinical trial of etripamil for the treatment of AFib-RVR. We may not be able to successfully expand the scope of cardiovascular indications for etripamil beyond PSVT, or leverage our expertise and experience with etripamil in PSVT to other product candidates. We may not be able to in-license, acquire or develop future product candidates that are safe and effective. Even if we are successful in continuing to expand etripamil to other indications and further build our pipeline, the potential product candidates that we identify may not be suitable for clinical development, including as a result of safety, tolerability, efficacy or other characteristics that indicate that they are unlikely to be drugs that will receive marketing approval, achieve market

acceptance or obtain reimbursements from third-party payors. If we do not successfully execute on our strategy of expanding our product pipeline, it could significantly harm our financial position and adversely affect the trading price of our common shares.

The development of additional product candidates is risky and uncertain.

Efforts to identify, acquire or in-license, and then develop product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our efforts may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development, approved products or commercial revenues for many reasons, including the following:

- the methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render any product candidates we develop obsolete;
- any product candidates we develop may nevertheless be covered by third parties' patents or other exclusive rights;
- a product candidate may be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by physicians, patients, the medical community or third-party payors.

We have limited financial and management resources and, as a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater market potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in circumstances under which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If we are unsuccessful in identifying and developing additional product candidates or are unable to do so, our business may be harmed.

Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and we cannot assure you that any ongoing, planned or future clinical trials will lead to results sufficient for the necessary regulatory approvals.

Success in preclinical testing and earlier clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Preclinical tests and Phase 1 and Phase 2 clinical trials are primarily designed to test safety, to study pharmacokinetics and pharmacodynamics and to understand the side effects of product candidates at various doses and schedules. Success in preclinical studies and earlier clinical trials does not ensure that later efficacy trials will be successful, nor does it predict final results. For example, our Phase 2 clinical trial of etripamil for PSVT was conducted in an electrophysiology lab, a controlled setting, in which episodes of supraventricular tachycardia, or SVT, were induced and etripamil was administered by healthcare providers. Our Phase 3 clinical trials are being conducted in an at-home setting with patients self-administering etripamil and monitoring their cardiac activity as episodes of SVT occur. Additionally, in our Phase 2 clinical trial, four sprays of study drug were dispensed to patients using four separate FDA approved single spray devices. In our Phase 3 clinical trials, patients self-administer two to four sprays of study drug from an FDA approved device that is capable of delivering two separate sprays. Accordingly, the results of our Phase 2 trial of etripamil may not be replicated in the at-home setting of our Phase 3 clinical trials, and while our RAPID Phase 3 trial did meet its primary endpoint, our NODE-301 clinical trial

did not meet its primary endpoint. Etripamil and any future product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through earlier clinical trials.

In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. Clinical trial design flaws are more likely in therapy areas, such as PSVT, where there are limited previous trials from which to learn and model clinical trials. As an organization, we have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

Our business, operations and clinical development timelines and plans have been adversely affected by the effects of health epidemics, such as the COVID-19 pandemic, and could be affected by future health epidemics.

Our business, operations and clinical development timelines and plans have been, and could in the future be adversely affected by health epidemics in regions where we have concentrations of clinical trial sites or other business operations, and could cause significant disruption in the operations of CROs and manufacturers upon whom we rely.

The COVID-19 pandemic resulted in many state, local and foreign governments implementing various quarantines, executive orders, shelter-in-place orders and similar government orders and restrictions in order to control the spread of the disease, which changing restrictions have resulted in periods of business closures, work stoppages, slowdowns and delays, work-from-home policies, travel restrictions and cancellation of events. These actions, and the uncertainty about the ever evolving landscape, could negatively impact productivity and disrupt our business and operations.

Further, if the business operations of our third-party manufacturers and suppliers are interrupted, this could disrupt our supply chain and impact our ongoing preclinical studies and clinical trials. In addition, disruptions or delays in chemistry, manufacturing and control activities for current or future product candidates in general may result in delays and challenges in numerous areas of the drug development lifecycle, including preclinical drug development, clinical stage validation and testing and manufacturing.

In addition, global health crises have in the past and could in the future result in future periods of significant disruption of global financial markets, which could reduce our ability to access capital, which could in the future negatively affect our liquidity. In addition, further recessions or market correction resulting from the sustained pandemic could materially affect our business and the value of our common shares.

We may encounter substantial delays or difficulties in our clinical trials.

We may not commercialize, market, promote or sell any product candidate without obtaining marketing approval from the FDA or comparable foreign regulatory authorities, and we may never receive such approvals. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans and will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

We may experience numerous unforeseen events prior to, during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize etripamil and any future product candidates, including:

- delays in reaching a consensus with regulatory authorities on design or implementation of our clinical trials;
- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, and clinical trial sites;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, patients may drop out of these clinical trials at a higher rate than we anticipate or fail to return for post-treatment follow-up or we may fail to recruit suitable patients to participate in a trial;
- clinical trials of our product candidates may produce negative or inconclusive results;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event, concerns with a class of product candidates or after an inspection of our clinical trial operations, trial sites or manufacturing facilities;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- interruptions resulting from public health emergencies, such as those related to the COVID-19 pandemic, or other geopolitical tensions, such as Russia's incursion into Ukraine; or
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue from future drug sales or other sources. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional testing to bridge our modified product candidate to earlier versions. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring competing drugs to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;

- have regulatory authorities withdraw, or suspend, their approval of the drug or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Our product development costs will also increase if we experience delays in testing or obtaining marketing approvals. We do not know whether any of our preclinical studies or clinical trials will begin as planned, need to be restructured or be completed on schedule, if at all.

Further, we, the FDA or an IRB may suspend our clinical trials at any time if it appears that we or our collaborators are failing to conduct a trial in accordance with regulatory requirements, including the FDA's current Good Clinical Practice, or GCP, regulations, that we are exposing participants to unacceptable health risks, or if the FDA finds deficiencies in our investigational new drug applications, or INDs, or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be negatively impacted, and our ability to generate revenues from our product candidates may be delayed.

Clinical trials are very expensive, time consuming and difficult to design and implement.

Our product candidates will require clinical testing before we are prepared to submit an NDA, or comparable application to foreign regulatory authorities, for regulatory approval. We cannot predict with any certainty if or when we might submit an application for regulatory approval for any of our product candidates or whether any such application will be approved by the FDA or foreign regulatory authority. Human clinical trials are very expensive and difficult to design and implement, in part because they are subject to rigorous regulatory requirements. For instance, the FDA or foreign regulatory authority may not agree with our proposed endpoints for any future clinical trial of our product candidates, which may delay the commencement of our clinical trials. In addition, we may not succeed in developing and validating disease relevant clinical endpoints based on insights regarding biological pathways for the diseases we are studying. The clinical trial process is also time consuming. We estimate that the successful completion of clinical trials for etripamil and any future product candidates will take several years to complete. Furthermore, failure can occur at any stage, and we could encounter problems that cause us to abandon or repeat clinical trials. For example, the pivotal NODE-301 trial of etripamil for PSVT did not meet its primary endpoint. As a result, we were required to submit a protocol amendment to the FDA for the RAPID trial.

Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be delayed, made more difficult or rendered impossible by multiple factors outside our control.

Identifying and qualifying patients to participate in our clinical trials is critical to our success. If the actual number of patients with PSVT, AFib-RVR or any other indications that we may pursue for etripamil or future product candidates, is smaller than we anticipate, we may encounter difficulties in enrolling patients in our clinical trials, thereby delaying or preventing development and approval of etripamil and any future product candidates. Even once enrolled we may be unable to retain a sufficient number of patients to complete any of our trials. Patient enrollment and retention in clinical trials depends on many factors, including the size of the patient population, the nature of the trial protocol, the existing body of safety and efficacy data, the number and nature of competing treatments and ongoing clinical trials of competing therapies for the same indication, the proximity of patients to clinical sites, the experience and capabilities of the clinical sites to recruit the correct patients, and the eligibility criteria for the trial. In our Phase 3 clinical trials, we are attempting to enroll elderly patients and patients taking concomitant medications that impact the heart, such as other calcium channel blockers and beta blockers. We are doing this in order to obtain efficacy and safety data on patients representing the subset of our intended population that is most vulnerable to safety concerns with the use of etripamil. Such patients may be

difficult to enroll in this trial, and the lack of data on these patients may negatively impact the approvability or labeling of etripamil. Patient enrollment may also be affected by COVID-19 or future pandemics, such as patients experiencing difficulty accessing clinical trial sites and complying with clinical trial protocols. For example, some sites for our NODE-303 study during the COVID-19 pandemic closed their practices to further enrollment.

In our Phase 2 clinical trial of etripamil for the treatment of PSVT, only 104 of 199 enrolled patients completed the trials, with 70 patients unable to induce or sustain episodes of SVT during the trial period. The first Phase 3 trial of PSVT for etripamil enrolled over 400 diagnosed patients with PSVT meeting inclusion and exclusion criteria in order to achieve the required treatment of 150 confirmed PSVT episodes. PSVT is episodic and unpredictable, and all of our Phase 3 trial designs depend on patients experiencing and recognizing an episode of SVT, self-administering etripamil and monitoring their cardiac activity using a monitoring device. We cannot control the timing of these episodes or guarantee that patients will correctly recognize the episode, self-administer etripamil and use the cardiac monitor as directed. We also cannot predict with certainty the number or timing of any SVT episodes for those patients that enroll in the trial. Conducting a Phase 3 clinical trial for a PSVT treatment in an at-home setting is paradigm changing, and subject to a number of risks. There is limited, if any, meaningful precedent from which to inform our trial design and make assumptions about patient enrollment and compliance. Accordingly, our Phase 3 trial design is subject to significantly more risks than if there were numerous studies upon which we could model our protocols. Our efficacy and safety databases could take significantly longer to populate than projected, which would add cost to our development program and delay any potential approval of etripamil.

Furthermore, our efforts to build relationships with patient communities may not succeed, which could result in delays in patient enrollment in our clinical trials. In addition, any negative results we may report in clinical trials of etripamil and any future product candidate may make it difficult or impossible to recruit and retain patients in other clinical trials of that same product candidate. For example, we reported a failed primary endpoint from our NODE-301 trial in March 2020. Delays or failures in planned patient enrollment or retention may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop etripamil or any future product candidates or could render further development impossible. In addition, we expect to rely on CROs and clinical trial sites to ensure proper and timely conduct of our future clinical trials and, while we intend to enter into agreements governing their services, we will be limited in our ability to compel their actual performance. Similarly, our formulation of etripamil is designed to be self-administered as a nasal spray during an SVT episode by patients enrolled in our Phase 3 trials, or during a AFib-RVR episode by patients in our Phase 2 trial. While we expect enrolled patients to adhere to the protocol, our ability to ensure patient compliance is limited.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit the commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts, to their doctor. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. Regulatory authorities may draw different conclusions or require additional testing to confirm these determinations, if they occur. For example, in our Phase 2 clinical trial for PSVT, three serious adverse events, or SAEs, were considered possibly related to etripamil, including an episode of second degree AV block that subsequently and spontaneously resolved. Calcium channel blockers have known side effects, such as slowing AV conduction, slowing the heart rate below normal levels and hypotension, or low blood pressure. While we designed etripamil to have a short pharmacodynamic effect to lower these risks, if etripamil is not quickly metabolized as designed, these known side effects may become more pronounced in patients who use etripamil.

In addition, it is possible that as we test etripamil or any future product candidates in larger, longer and more extensive clinical trials, such as our Phase 3 clinical trials, or as use of etripamil or any future product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by subjects or patients. Many times, side effects are only detectable after investigational drugs are tested in large-scale pivotal trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that etripamil or any future product candidates have side effects or causes serious or life-threatening

side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

Interim, "top-line" and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publish interim, "topline" or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or "topline" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common shares to fluctuate significantly.

As an organization, we have completed pivotal clinical trials, but we have never successfully submitted an NDA. We may be unable to do so for any product candidates we may develop.

After completing pivotal clinical trials, we will need to obtain the approval of the FDA and other regulatory agencies to market etripamil or any of our other product candidates. Carrying out later-stage clinical trials and the submission of a successful NDA is a complicated process. As an organization, we have completed two Phase 3 clinical trials, we have other trials ongoing, and we have limited experience in preparing, submitting and prosecuting regulatory filings. Due to our limited experience with completing later stage trials, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to NDA submission and approval of etripamil for the treatment of PSVT. Even if we submit the NDA for etripamil for PSVT, the FDA may refuse to file it or issue a complete response letter rather than approval for commercial marketing. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials could prevent us from or delay us in commercializing etripamil for the treatment of PSVT or AFIB-RVR.

We may explore additional strategic collaborations that may never materialize, or we may be required to relinquish important rights to and control over the development of our product candidates to any future collaborators.

We intend to continue to periodically explore a variety of possible strategic collaborations in an effort to gain access to additional product candidates or resources. We are likely to face significant competition in seeking appropriate strategic collaborators, and strategic collaborations can be complicated and time consuming to negotiate and document. We may not be able to negotiate strategic collaborations on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic collaborations because of the numerous risks and uncertainties associated with establishing them.

Future collaborations could subject us to a number of risks, including:

- we may be required to undertake the expenditure of substantial operational, financial and management resources;
- we may be required to issue equity securities that would dilute our shareholders' percentage ownership of our company;
- we may be required to assume substantial actual or contingent liabilities;
- we may not be able to control the amount and timing of resources that our strategic collaborators devote to the development or commercialization of our product candidates;

- strategic collaborators may select indications or design clinical trials in a way that may be less successful than if we were doing so;
- strategic collaborators may delay clinical trials, provide insufficient funding, terminate a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new version of a product candidate for clinical testing;
- strategic collaborators may not pursue further development of products resulting from the strategic collaboration arrangement or may elect to discontinue research and development programs;
- strategic collaborators may not commit adequate resources to the marketing and distribution of our product candidates, limiting our potential revenues from these products;
- disputes may arise between us and our strategic collaborators that result in the delay or termination of the research or development of our product candidates or that result in costly litigation or arbitration that diverts management's attention and consumes resources;
- strategic collaborators may experience financial difficulties;
- strategic collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in a manner that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- business combinations or significant changes in a strategic collaborator's business strategy may adversely affect a strategic collaborator's willingness or ability to complete its obligations under any arrangement;
- strategic collaborators could decide to move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors; and
- strategic collaborators could terminate the arrangement or allow it to expire, which would delay the development and may increase the cost of developing our product candidates.

Risks Related to the Commercialization of Our Product Candidates

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell etripamil or any future product candidates, we may not be successful in commercializing etripamil or any future product candidates, if and when they are approved.

To successfully commercialize etripamil or any future product candidate that may result from our development programs, we will need to build out our sales and marketing capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract field force to market any product candidate we may develop will be expensive and time consuming and could delay any drug launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may seek to enter into collaborations with other entities to use their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we may be unable to generate sufficient revenue to sustain our business. We may compete with many companies that currently have extensive, experienced, and well-funded marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We will likely also face competition if we seek third parties to assist us with the sales and marketing efforts of etripamil and any future product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

Even if etripamil or any future product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.

Even if etripamil or any future product candidates receive marketing approval, they may fail to gain market acceptance by physicians, patients, third-party payors and others in the medical community. If such product candidates do not achieve an adequate level of acceptance, we may not generate significant drug revenue and may not become profitable. The degree of market acceptance of etripamil or any future product candidates, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the convenience and ease of administration compared to alternative treatments and therapies;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the efficacy and potential advantages compared to alternative treatments and therapies;
- the effectiveness of sales and marketing efforts;
- the prevalence and severity of any side effects;
- the strength of our relationships with patient communities;
- the cost of treatment in relation to alternative treatments and therapies, including any similar generic treatments;
- our ability to offer such drug for sale at competitive prices;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement; any restrictions on the use of the drug together with other medications; and the awareness and support from key opinion leaders in cardiology.

Our efforts to educate physicians, patients, third-party payors and others in the medical community on the benefits of etripamil or any future product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the potential of etripamil to shift the treatment paradigm away from acute-care settings to self-administration. Because we expect sales of etripamil or any future product candidates, if approved, to generate substantially all of our revenues for the foreseeable future, the failure of these product candidates to find market acceptance would harm our business.

Even if we successfully obtain approval for etripamil, its success will be dependent on its proper use.

While we have designed etripamil to be self-administered, we cannot control the successful use of the product. While we have conducted, and intend in the future to conduct, human factors studies to determine how to optimize the instructions for use, the results in our clinical trials may not be replicated by users in the future. If we are not successful in promoting the proper use of etripamil, if approved, we may not be able to achieve market acceptance or effectively commercialize the drug. In addition, even in the event of proper use of etripamil, individual devices may fail. Increasing the scale of production inherently creates increased risk of manufacturing errors, and we may not be able to adequately inspect every device that is produced, and it is possible that individual devices may fail to perform as designed. Manufacturing errors could negatively impact market acceptance of any of our product candidates that receive approval, result in negative press coverage, or increase our liability.

If the market opportunities for etripamil and any future product candidates are smaller than we estimate, our business may suffer.

Our eligible patient population may differ significantly from the actual market addressable by our product candidates. Our projections of both the number of people who have these conditions, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, insurance claims databases or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of these diseases. The number of patients may turn out to be lower than expected. Likewise, the potentially addressable patient population for each of our product candidates may be limited or may not be amenable to treatment with our product candidates, and new patients may become increasingly difficult to identify or access. If the market opportunities for our product candidates are smaller than we estimate, our business and results of operations could be adversely affected.

We may face substantial competition, which may result in others developing or commercializing drugs before or more successfully than us.

The development and commercialization of new drugs is highly competitive. We may face competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

More established companies may have a competitive advantage over us due to their greater size, resources and institutional experience. In particular, these companies have greater experience and expertise in securing reimbursement, government contracts and relationships with key opinion leaders, conducting testing and clinical trials, obtaining and maintaining regulatory approvals and distribution relationships to market products and marketing approved drugs. These companies also have significantly greater research and marketing capabilities than we do. If we are not able to compete effectively against existing and potential competitors, our business and financial condition may be harmed.

As a result of these factors, our competitors may obtain regulatory approval of their drugs before we are able to, which may limit our ability to develop or commercialize etripamil and any future product candidates. Our competitors may also develop therapies that are safer, more effective, more widely accepted or less expensive than ours, and may also be more successful than we in manufacturing and marketing their drugs. These advantages could render our product candidates obsolete or non-competitive before we can recover the costs of such product candidates' development and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If we commercialize etripamil or any future product candidates outside of the United States, a variety of risks associated with international operations could harm our business.

We intend to seek approval to market etripamil outside of the United States and may do so for future product candidates. If we market approved products outside of the United States, we expect that we will be subject to additional risks in commercialization including:

- different regulatory requirements for approval of therapies in foreign countries;
- reduced protection for intellectual property rights;

- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- foreign reimbursement, pricing and insurance regimes;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from pandemics and public health emergencies, including those related to COVID-19 coronavirus, geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by many of the individual countries in and outside of Europe with which we will need to comply. Many biopharmaceutical companies have found the process of marketing their own products in foreign countries to be very challenging.

The pharmaceutical industry in China is highly regulated, and such regulations are subject to change, which may negatively affect the commercialization of the Company's medicines and drug candidates in that country.

On May 15, 2021, the Company entered into a license and collaboration agreement, or the License Agreement, with Ji Xing, which is an entity affiliated with RTW Investments, LP (RTW), an existing shareholder. Under the License Agreement, the Company granted Ji Xing exclusive development and commercialization rights to any pharmaceutical product that uses a device to deliver the Company's proprietary calcium channel blocker known as etripamil by nasal spray for all prophylactic and therapeutic uses in humans in the following territories: People's Republic of China, including mainland China, Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan (the Territory). The pharmaceutical industry in China is subject to comprehensive government regulation and supervision, encompassing the approval, registration, manufacturing, packaging, licensing and marketing of new medicines. In recent years, the regulatory framework in China for pharmaceutical companies has undergone significant changes, which the Company expects will continue. Any such change may cause delays in or prevent the successful research, development, manufacturing or commercialization of etripamil in the greater China region and may reduce the current benefits the Company believes are available to it from licensing such products to be developed, manufactured and sold in the greater China region. In addition, any failure by the Company or its partners to maintain compliance with applicable laws and regulations or obtain and maintain required licenses and permits may result in the suspension or termination of its business activities in China or create other legal risks.

Coverage and adequate reimbursement may not be available for etripamil or any future product candidates, which could make it difficult for us to gain market acceptance.

Market acceptance and sales of any product candidates that we commercialize, if approved, will depend in part on the extent to which reimbursement for these drugs and related treatments will be available from third-party payors, including government health administration authorities, managed care organizations and other private health insurers. Third-party payors decide for which therapies and establish reimbursement levels. While no uniform policy for coverage and reimbursement exists in the United States, third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage

and amount of reimbursement to be provided for any product candidates that we develop will be made on a payor-by-payor basis. Therefore, one payor's determination to provide coverage for a drug does not assure that other payors will also provide coverage, and adequate reimbursement, for the drug. Additionally, a third-party payor's decision to provide coverage for a therapy does not imply that an adequate reimbursement rate will be approved. Each payor determines whether or not it will provide coverage for a therapy, what amount it will pay the manufacturer for the therapy, and on what tier of its formulary it will be placed. The position on a payor's list of covered drugs, or formulary, generally determines the co-payment that a patient will need to make to obtain the therapy and can strongly influence the adoption of such therapy by patients and physicians. Patients who are prescribed treatments for their conditions and providers prescribing such services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that coverage and reimbursement will be available for any drug that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Inadequate coverage and reimbursement may impact the demand for, or the price of, any drug for which we obtain marketing approval. If coverage and adequate reimbursement are not available, or are available only to limited levels, we may not be able to successfully commercialize etripamil or any future product candidates that we develop.

In addition, we expect that the increased emphasis on managed care and cost containment measures in the United States by third-party payors and government authorities to continue and will place pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future. If we are unable to obtain and maintain sufficient third-party coverage and adequate reimbursement for our drug products, the commercial success of our drug products may be greatly hindered and our financial condition and results of operations may be materially and adversely affected.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidates that we may develop.

We face an inherent risk of product liability exposure related to the testing of etripamil or any future product candidates in clinical trials and may face an even greater risk if we commercialize any product candidate that we may develop. If we cannot successfully defend ourselves against claims that any such product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal of clinical trial participants;
- increased insurance costs;
- the inability to commercialize any product candidate that we may develop; and injury to our reputation and significant negative media attention.

Although we maintain clinical trial liability insurance coverage with maximum coverage of $10 million per incident and an aggregate loss limit of $10 million such insurance may not be adequate to cover all liabilities that we may incur with a

medical product during the clinical trials. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and maintain a product liability insurance if we successfully commercialize any product candidate. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Risks Related to Regulatory Compliance

Even if we obtain and maintain approval for etripamil or any future product candidates from the FDA, we may never obtain approval of etripamil or any future product candidates outside of the United States, which would limit our market opportunities and could harm our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of etripamil or any future product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable foreign regulatory authorities also must approve the manufacturing and marketing of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for any product candidates, if approved, is also subject to approval. Obtaining approval for etripamil or any future product candidates in the European Union from the European Commission following the opinion of the European Medicines Agency, if we choose to submit a marketing authorization application there, would be a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission, as the case may be, may limit the indications for which the drug may be marketed, require extensive warnings on the drug labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of etripamil or any future product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of etripamil or any future product candidates will be harmed and our business, financial condition, results of operations and prospects could be harmed.

Even if we obtain regulatory approval for etripamil or any future product candidates, they will remain subject to ongoing regulatory oversight.

Even if we obtain regulatory approvals for etripamil or any future product candidates, such approvals will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for etripamil or any future product candidates may also be subject to a REMS, limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 trials, and surveillance to monitor the quality, safety and efficacy of the drug. Such regulatory requirements may differ from country to country depending on where we have received regulatory approval.

In addition, drug manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the NDA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a drug, such as adverse events of unanticipated severity or frequency, or problems with the facility where the drug is manufactured or if a regulatory authority disagrees with the promotion, marketing or labeling of that

drug, a regulatory authority may impose restrictions relative to that drug, the manufacturing facility or us, including requesting a recall or requiring withdrawal of the drug from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of etripamil or any future product candidates, a regulatory authority may:

- issue an untitled letter or warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or comparable foreign marketing application or any supplements thereto submitted by us or our partners;
- restrict the marketing or manufacturing of the drug;
- seize or detain the drug or otherwise require the withdrawal of the drug from the market;
- refuse to permit the import or export of product candidates; or
- refuse to allow us to enter into supply contracts, including government contracts.

Moreover, the FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. Physicians, on the other hand, may prescribe products for off-label uses. Although the FDA and other regulatory agencies do not regulate a physician's choice of drug treatment made in the physician's independent medical judgment, they do restrict promotional communications from companies or their sales force with respect to off-label uses of products for which marketing clearance has not been issued. However, biopharmaceutical companies may share truthful and not misleading information that is otherwise consistent with the labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize etripamil or any future product candidates and harm our business, financial condition, results of operations and prospects.

The FDA's and other regulatory authorities' policies may change, and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

In addition, we cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad.

Our relationships with customers, physicians, and third-party payors are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and security laws, and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Healthcare providers, including physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors subject us to various federal and state fraud and abuse laws, data privacy and security laws, transparency laws and other healthcare laws that may constrain the business or financial arrangements and relationships through which we research, sell, market, and distribute our products, if we obtain marketing approval.

The federal Anti-Kickback Statute prohibits the offer, receipt, or payment of remuneration in exchange for or to induce the referral of patients or the use of products or services that would be paid for in whole or part by Medicare, Medicaid or other federal healthcare programs. Remuneration has been broadly defined to include anything of value, including cash, improper discounts, and free or reduced price items and services. Additionally, the intent standard under the federal Anti-Kickback Statute was amended by the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, PPACA, to a stricter standard such that a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. Further, PPACA codified case law that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act.

The federal false claims, including the False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment of federal funds, and knowingly making, or causing to be made, a false record or statement material to a false or fraudulent claim to avoid, decrease or conceal an obligation to pay money to the federal government.

The federal Health Information Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.

HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, also imposes, among other things, certain standards and obligations on covered entities including certain healthcare providers, health plans and healthcare clearinghouses, and their respective business associates that create, receive, maintain, or transmit individually identifiable health information for or on behalf of a covered entity as well as their covered subcontractors relating to the privacy, security, transmission and breach reporting of individually identifiable health information.

The federal Physician Payments Sunshine Act, and its implementing regulations, require certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to Centers for Medicare & Medicaid Services information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members.

We will also be subject to healthcare regulation and enforcement by the U.S. federal government and the states and any other countries in which we conduct our business, including our research, and the sales, marketing and distribution of our product candidates and products once they have obtained marketing authorization.

Analogous state and foreign anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, or that apply regardless of payor; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state and local laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; state laws that require the reporting of information related to drug pricing; state and local laws requiring the registration of pharmaceutical sales representatives; and state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Ensuring that our business arrangements with third parties comply with applicable healthcare laws and regulations will likely be costly. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm and the curtailment or restructuring of our operations.

If the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. Even if resolved in our favor, litigation or other legal proceedings relating to healthcare laws and regulations may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, manufacturing, sales, marketing or distribution activities. Uncertainties resulting from the initiation and continuation of litigation or other proceedings relating to applicable healthcare laws and regulations could have a material adverse effect on our ability to compete in the marketplace.

Healthcare legislative reform measures may have a negative impact on our business and results of operations.

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, in March 2010 the PPACA, was passed, which substantially changed the way healthcare is financed by both governmental and private payors in the United States. There have been executive, judicial and Congressional challenges to certain aspects of the PPACA. For example, the Tax Cuts and Jobs Act of 2017, or the Tax Act, was enacted, which included a provision that repealed, effective January 1, 2019, the tax based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the PPACA mandated "Cadillac" tax on high cost employer sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the PPACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Further, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in PPACA marketplaces through plan year 2025. The IRA also eliminates the "donut hole" under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. It is possible that the PPACA will be subject to judicial or Congressional challenges

in the future. It is unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the PPACA and our business.

Further, in the United States there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under government payor programs, and review the relationship between pricing and manufacturer patient programs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. More recently, in July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, the U.S. Department of Health and Human Services, or HHS, released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. Further, the IRA, among other things (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. It is currently unclear how the IRA will be implemented but is likely to have a significant impact on the pharmaceutical industry. Additionally, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. We expect that additional U.S. healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for etripamil or any future product candidates or additional pricing pressures.

In addition, other legislative changes have been proposed and adopted since the PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which includes reductions to Medicare payments to providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect until 2031 unless additional Congressional action is taken. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

We cannot predict the likelihood, nature or extent of health reform initiatives that may arise from future legislation or administrative action in the United States or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing or new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, etripamil or any future product candidates we may develop may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our business involves the use of hazardous materials and we and our third-party manufacturers and suppliers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our research and development activities and our third-party manufacturers' and suppliers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of etripamil and any future product candidates and other hazardous compounds. We and our manufacturers and suppliers are subject to laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending

their use and disposal. We cannot eliminate the risk of contamination, which could cause an interruption of our commercialization efforts, research and development efforts and business operations, environmental damage resulting in costly clean-up and liabilities under applicable laws and regulations governing the use, storage, handling and disposal of these materials and specified waste products. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials generally comply with the standards prescribed by these laws and regulations, we cannot guarantee that this is the case or eliminate the risk of accidental contamination or injury from these materials. In such an event, we may be held liable for any resulting damages and such liability could exceed our resources and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. We do not currently carry hazardous waste insurance coverage.

Risks Related to Our Dependence on Third Parties

We will rely on third parties to produce clinical and commercial supplies of etripamil and any future product candidates.

We do not own or operate facilities for drug manufacturing, storage and distribution, or testing. We are dependent on third parties to manufacture the clinical supplies of etripamil and any future product candidates. The facilities used by our contract manufacturers to manufacture etripamil and any future product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs for manufacture of active drug substances, nasal spray device, and finished product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we will not be able to secure and/or maintain regulatory approval for our product candidates. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. We intend to use multiple contract manufacturers for clinical and commercial supply of our drug product and drug substance. As such, we will need to demonstrate to the FDA that the drug product and drug substance from these contract manufacturers are comparable, which may include conducting additional equivalence studies. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates.

Further, we also will rely on third-party manufacturers to supply us with sufficient quantities of etripamil and any future product candidates, if approved, for commercialization. We do not yet have a commercial supply agreement for commercial quantities of drug substance, drug product or nasal spray device. If we are not able to meet market demand for any approved product, it would negatively affect our ability to generate revenue, harm our reputation, and could have a material and adverse effect on our business and financial condition. Increasing the scale of production inherently creates increased risk of manufacturing errors, and we may not be able to adequately inspect every device that is produced, and it is possible that individual devices may fail to perform as designed. Manufacturing errors could negatively impact market acceptance of any of our product candidates that receive approval, result in negative press coverage, or increase our liability.

Further, our reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including:

- inability to meet our product specifications and quality requirements consistently;
- delay or inability to procure or expand sufficient manufacturing capacity;

- issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- our third-party manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately;
- our third-party manufacturers may fail to comply with cGMP-compliance and other inspections by the FDA or other comparable regulatory authorities;
- our inability to negotiate manufacturing agreements with third parties under commercially reasonable terms, if at all;
- breach, termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- reliance on a single source for the nasal spray device;
- our third-party manufacturers may not devote sufficient resources to our product candidates;
- we may not own, or may have to share, the intellectual property rights to any improvements made by our third-party manufacturers in the manufacturing process for our product candidates;
- operations of our third party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including public health emergencies, natural disasters, such as earthquakes, fires or floods, the bankruptcy of the manufacturer or supplier, carrier disruptions or increased costs that are beyond our control, and global macro uncertainty related to the Ukraine – Russia crisis.

In addition, if we enter into a strategic collaboration with a third party for the commercialization of etripamil or any future product candidate, we will not be able to control the amount of time or resources that they devote to such efforts. If any strategic collaborator does not commit adequate resources to the marketing and distribution of etripamil or any future product candidate, it could limit our potential revenues.

Any of these events could lead to clinical trial delays, failure to obtain regulatory approval or affect our ability to successfully commercialize etripamil or any future product candidates once approved. Some of these events could be the basis for FDA action, including injunction, request for recall, seizure, or total or partial suspension of production.

We rely on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We have engaged CROs to conduct our Phase 3 clinical trials of etripamil for the treatment of PSVT, and our Phase 2 clinical trial of etripamil for the treatment of AFib-RVR, and we expect to engage a CRO for future clinical trials of etripamil and any future product candidates. We do not currently have the ability to independently conduct any clinical trials. We rely on CROs and clinical trial sites to ensure the proper and timely conduct of our preclinical studies and clinical trials, and we expect to have limited influence over their actual performance. We rely upon CROs to monitor and manage data for our clinical programs, as well as the execution of future nonclinical studies. We expect to control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the good laboratory practices, or GLPs, and GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities in the form of International Conference on Harmonization guidelines for any of our product candidates that are in preclinical and clinical development. The

regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. Although we rely on CROs to conduct GCP-compliant clinical trials, we remain responsible for ensuring that each of our GLP preclinical studies and clinical trials is conducted in accordance with its investigational plan and protocol and applicable laws and regulations, and our reliance on the CROs does not relieve us of our regulatory responsibilities. If we or our CROs fail to comply with GCPs, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of subjects, we may be required to repeat clinical trials, which would delay the regulatory approval process.

Our reliance on third parties to conduct clinical trials will result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Any failure by third parties to prevent unauthorized access, use or disclosure of data, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information.

Communicating with CROs and other third parties can be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Such parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- experience business disruptions from public health emergencies, such as the COVID-19 pandemic, and accompanying shelter in place orders; or
- undergo changes in priorities or become financially distressed.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, fail to comply with regulatory requirements, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, any product candidate that we develop. As a result, our financial results and the commercial prospects for any product candidate that we develop would be harmed, our costs could increase, and our ability to generate revenue could be delayed. While we will have agreements governing their activities, our CROs will not be our employees, and we will not control whether or not they devote sufficient time and resources to our future clinical and nonclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities that could harm our business. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may reduce our trade secret protection and allow our potential competitors to access and exploit our proprietary technology.

If our relationship with any of these CROs terminates, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can negatively affect our ability to meet our desired clinical development timelines. Though we intend to manage carefully our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a negative impact on our business, financial condition and prospects.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval of etripamil and any future product candidates.

Etripamil is intended to be used with a nasal-spray device, which may result in additional regulatory and supply risks.

Etripamil is administered through a nasal-spray device that we obtain from a single source supplier, and that supplier is relying on multiple component suppliers, some of whom are single source suppliers. There are a limited number of device suppliers that address our particular design requirements. While we intend to explore alternative nasal spray devices for the delivery of etripamil that are produced by other suppliers to have backup sources for future commercial needs, we may not identify other nasal device suppliers that meet our requirements, and such alternative devices may not be as effective at the delivery of etripamil as our current supplier's device. We do not currently have a formal supply agreement with our current sole nasal spray device supplier, and obtain such devices as needed. Even if we reach agreement for commercial supply, if we do not have additional nasal spray device suppliers, our sole supplier may be unable to meet our demands. Unpredictability of supply could have a material adverse effect on our commercialization plans for etripamil, if approved, and could have a material adverse effect on our business and financial condition.

Our finished drug product in the intra-nasal delivery system will be regulated as a drug/device combination product. We may experience delays in obtaining regulatory approval of etripamil given the increased complexity of the review process when approval of the product and a delivery device is sought under a single marketing application. In the United States, each component of a combination product is subject to the requirements established by the FDA for that type of component, whether a drug, biologic, or device. The delivery system device would be subject to FDA device requirements regarding design, performance and validation as well as human factors testing, among other things.

Delays in or failure of the studies conducted by us, or failure of our company, our collaborators, if any, or the third-party providers or suppliers to obtain or maintain regulatory approval could result in increased development costs, delays in or failure to obtain regulatory approval, and associated delays in etripamil reaching the market. Further, failure to successfully develop or supply the device, or to gain or maintain its approval, could adversely affect sales of etripamil.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for etripamil or any future product candidates, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize drugs similar or identical to ours, and our ability to commercialize successfully our product candidates may be impaired.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to etripamil and any future product candidates. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates. The patent application and prosecution process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. We may also fail to identify patentable aspects of our research and development before it is too late to obtain patent protection. Therefore, these and any of our patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, such as with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If any future licensors or licensees are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised and we might not be able to prevent third parties from making, using and selling competing products. If there are material defects in the form or preparation of our patents or patent applications, such patents or applications may be invalid and unenforceable. Moreover, our competitors may independently develop

equivalent knowledge, methods and know-how. Any of these outcomes could impair our ability to prevent competition from third parties.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds and technologies commonly involves complex legal and factual questions, which has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Furthermore, recent changes in patent laws in the United States, including the America Invents Act of 2011, may affect the scope, strength and enforceability of our patent rights or the nature of proceedings that may be brought by us related to our patent rights.

We may not be aware of all third-party intellectual property rights potentially relating to etripamil or any future product candidates. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. For example, U.S. applications filed before November 28, 2000 and certain U.S. applications filed after that date that will not be filed outside the United States remain confidential until a patent issues. Therefore, we cannot be certain that we were the first to make the inventions claimed in our patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, should we own any patents or patent applications in the future, we may not be certain that we were the first to file for patent protection for the inventions claimed in such patents or patent applications. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Moreover, we may be subject to a third-party pre-issuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, reexamination, inter parties review, post grant review, or interference proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Our pending and future patent applications may not result in patents being issued that protect our technology or product candidates, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection against competing products or processes sufficient to achieve our business objectives, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may seek to market generic versions of any approved products by submitting abbreviated new drug applications to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable and/or not infringed. Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and/or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and/or unenforceable.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will have to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned patents and/or applications and any patent rights we may own or license in the future. We rely on our outside counsel to pay these fees due to non-U.S. patent agencies. The USPTO and various non-U.S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply.

Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our products or technologies, we may not be able to stop a competitor from marketing products that are the same as or similar to etripamil or any future product candidates, which would have a material adverse effect on our business. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market and this circumstance could harm our business.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, such as etripamil, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their drug earlier than might otherwise be the case.

Intellectual property rights do not necessarily address all potential threats to our business.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business. The following examples are illustrative:

- others may be able to make compounds or formulations that are similar to etripamil or formulations of etripamil or our future product candidates but that are not covered by the claims of any patents, should they issue, that we own or control;
- we or any strategic partners might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or control;
- we might not have been the first to file patent applications covering certain of our inventions;

- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or control may not provide us with any competitive advantages, or may be held invalid or unenforceable as a result of legal challenges;
- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where we do not have patent rights and then use the information learned from such activities to develop competitive drugs for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and the patents of others may have an adverse effect on our business.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property rights, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents, future trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, trademarks, copyrights or other intellectual property. In addition, in a patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patents do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

In any infringement litigation, any award of monetary damages we receive may not be commercially valuable. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing, misappropriating or successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a negative impact on our ability to compete in the marketplace.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could have a negative impact on the success of our business.

Our commercial success depends, in part, upon our ability and the ability of future collaborators, if any, to develop, manufacture, market and sell etripamil and any future product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to etripamil and any future product candidates and technology, including interference proceedings, post grant review and inter partes review before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could have a negative impact on our ability to commercialize our current and any future product candidates. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidate(s) and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidate. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. A finding of infringement could prevent us from manufacturing and commercializing etripamil or any future product candidates or force us to cease some or all of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects. See the section herein titled "Legal Proceedings" for additional information.

We may need to license intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property rights, including patent rights, that are important or necessary to the development of etripamil or any future product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms, or at all, and we could be forced to accept unfavorable contractual terms. If we are unable to obtain such licenses on commercially reasonable terms, our business could be harmed.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications, as a result of the work they performed on our behalf. Although it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own, and we cannot be certain that our agreements with such parties will be upheld in the face of a potential challenge or that they will not be breached, for which we may not have an adequate remedy. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property.

Changes in U.S. patent law or the patent law of other countries or jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect etripamil and any future product candidates.

The United States has recently enacted and implemented wide ranging patent reform legislation. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce patents that we have licensed or that we might obtain in the future. Similarly, changes in patent law and regulations in other countries or jurisdictions, changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we have licensed or that we may obtain in the future. For example, the complexity and uncertainty of European patent laws have also increased in recent years. In Europe, a new unitary patent system is scheduled to be introduced by June 1, 2023, which would significantly impact European patents, including those granted before the introduction of such a system. Under the unitary patent system, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court (UPC). As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation. Patents granted before the implementation of the UPC will have the option of opting out of the jurisdiction of the UPC and remaining as national patents in the UPC countries. Patents that remain under the jurisdiction of the UPC will be potentially vulnerable to a single UPC-based revocation challenge that, if successful, could invalidate the patent in all countries who are signatories to the UPC. We cannot predict with certainty the long-term effects of any potential changes.

We may not be able to protect our intellectual property rights throughout the world, which could negatively impact our business.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. In some cases, we may not be able to obtain patent protection for certain technology outside the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States, even in jurisdictions where we do pursue patent protection. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we do pursue patent protection or from selling or importing products made using our inventions in and into the United States or other jurisdictions.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents, if pursued and obtained, or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful.

Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

The ongoing conflict in Ukraine and related sanctions could significantly devalue our Russian and Ukrainian patents. Recent Russian decrees may significantly limit our ability to enforce Russian patents. We cannot predict when or how this situation will change.

Reliance on third parties requires us to share our proprietary information, which increases the possibility that such information will be misappropriated or disclosed.

Because we rely on third parties to develop and manufacture etripamil and any future product candidates, or if we collaborate with third parties for the development or commercialization of etripamil or any future product candidates, we must, at times, share proprietary information with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share confidential information increases the risk that such information become known by our competitors, is inadvertently incorporated into the technology of others, or is disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how, a competitor's discovery of our know-how or other unauthorized use or disclosure could have an adverse effect on our business and results of operations.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our know-how. Despite our efforts to protect our know-how, we may not be able to prevent the unauthorized disclosure or use of our technical know-how by the parties to these agreements. Moreover, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our confidential information or proprietary technology and processes. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees, contractors and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation. Moreover, if confidential information that is licensed or disclosed to us by our partners, collaborators, or others is inadvertently disclosed or subject to a breach or violation, we may be exposed to liability to the owner of that confidential information. Enforcing a claim that a third-party illegally obtained and is using our proprietary information, like patent litigation, is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect proprietary information.

Any trademarks we may obtain may be infringed or successfully challenged, resulting in harm to our business.

We expect to rely on trademarks as one means to distinguish any of our product candidates that are approved for marketing from the products of our competitors. We have not yet selected trademarks for etripamil and have not yet begun the process of applying to register trademarks for etripamil or any other product candidate. Once we select trademarks and apply to register them, our trademark applications may not be approved. Third parties may oppose our trademark applications or otherwise challenge our use of the trademarks. In the event that our trademarks are successfully challenged, we could be forced to rebrand our products, which could result in loss of brand recognition and could require us to devote resources to advertising and marketing new brands. Our competitors may infringe our trademarks, and we may not have adequate resources to enforce our trademarks.

In addition, any proprietary name we propose to use with etripamil or any future product candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

If we are unable to protect the confidentiality of our proprietary information, our business and competitive position would be harmed.

In addition to seeking patent and trademark protection for etripamil and any future product candidate, we also rely on unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our proprietary information, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information. Monitoring unauthorized uses and disclosures of our intellectual property is difficult, and we do not know whether the steps we have taken to protect our intellectual property will be effective. In addition, we may not be able to obtain adequate remedies for any such breaches. Enforcing a claim that a party illegally disclosed or misappropriated proprietary information is difficult, expensive and time consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets.

Moreover, our competitors may independently develop knowledge, methods and know-how equivalent to our proprietary information. Competitors could purchase our products and replicate some or all of the competitive advantages we derive from our development efforts for technologies on which we do not have patent protection. If any of our proprietary information were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our proprietary information were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We also seek to preserve the integrity and confidentiality of our data and other confidential information by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached and detecting the disclosure or misappropriation of confidential information and enforcing a claim that a party illegally disclosed or misappropriated confidential information is difficult, expensive and time-consuming, and the outcome is unpredictable. Further, we may not be able to obtain adequate remedies for any breach. In addition, our confidential information may otherwise become known or be independently discovered by competitors, in which case we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.

We are highly dependent on our President and Chief Executive Officer, Joseph Oliveto, our Chief Medical Officer, David Bharucha, our Chief Commercial Officer, Lorenz Muller and our Chief Financial Officer, Amit Hasija. Each of them may currently terminate their employment with us at any time. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives. We do not currently maintain “key person” life insurance on the lives of our executives or any of our employees other than on our President and Chief Executive Officer, Joseph Oliveto.

Recruiting and retaining qualified scientific and clinical personnel and, if we progress the development of any of our product candidates, commercialization, manufacturing and sales and marketing personnel, will be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize our product candidates. Competition to hire from this

limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high-quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2022, we had 39 full-time employees. As the clinical development of etripamil progresses and as we expand our pipeline, we may experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of research, drug development, regulatory affairs and, if etripamil or any future product candidates receives marketing approval, sales, marketing and distribution. To manage any future growth, we will be required to continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with growth, we may not be able to effectively manage any expansion of our operations or recruit and train additional qualified personnel. Any expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a significant disruption of our product development programs and our ability to operate our business effectively.

Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Cyber-attacks are increasing in their frequency, sophistication, and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering, and other means to affect service reliability and threaten the confidentiality, integrity, and availability of information. Cyber-attacks also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient.

While we have not experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials by us or our CROs could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Additionally, any such event that leads to unauthorized access, use or disclosure of personal information, including personal information regarding our patients or employees, could harm our reputation, cause us not to comply with federal and/or state breach notification laws and foreign law equivalents and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information. Security breaches and other inappropriate access can be difficult to detect, and any delay in identifying them may lead to increased harm of the type described above. While we have implemented security measures to protect our information technology systems and infrastructure, such measures may not prevent service interruptions or security breaches that could adversely affect our business and to the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

If we fail to comply with European data protection laws, including the European Union General Data Protection Regulation 2016/679, or GDPR, when appropriate, and any other existing or future data protection regulations, our business, financial condition, results of operations and prospects may be materially adversely affected.

We anticipate seeking regulatory approval for, and commercialize, etripamil for the treatment of PSVT in Europe. We may also elect to do so for future product candidates. We are conducting clinical trial activities in Europe, which will subject us to European data protection laws, including the GDPR. The GDPR establishes requirements applicable to the processing of personal data (i.e., data which identifies an individual or from which an individual is identifiable). The GDPR creates significant and complex compliance burdens for companies such as: limiting permitted processing of personal data to only that which is necessary for specified, explicit and legitimate purposes; requiring the establishment a legal basis for processing personal data; expressly confirming that 'pseudonymized' or key-coded data constitutes personal data to which the GDPR applies; creating obligations for controllers and processors to appoint data protection officers in certain circumstances; increasing transparency obligations to data subjects for controllers (including presentation of certain information in a concise, intelligible and easily accessible form about how their personal data is used and their rights vis-à-vis that data and its use); introducing the obligation to carry out so-called data protection impact assessments in certain circumstances; establishing limitations on collection and retention of personal data through 'data minimization' and 'storage limitation' principles; establishing obligations to implement 'privacy by design'; introducing obligations to honor increased rights for data subjects (such as rights for individuals to be 'forgotten,' rights to data portability, rights to object etc. in certain circumstances); formalizing a heightened and codified standard of data subject consent; establishing obligations to implement certain technical and organizational safeguards to protect the security and confidentiality of personal data; introducing obligations to agree to certain specific contractual terms and to take certain measures when engaging third-party processors and joint controllers; introducing the obligation to provide notice of certain significant personal data breaches to the relevant supervisory authority(ies) and affected individuals; and mandating the appointment of representatives in the United Kingdom and/or European Union in certain circumstances. The processing of "special category personal data", such as health information, may also impose heightened compliance burdens under the GDPR. The GDPR has robust regulatory enforcement and penalties for noncompliance, including fines of up to €20 million or 4% of global annual revenue of any noncompliant company for the preceding financial year, whichever is higher. In addition to administrative fines, a wide variety of other potential enforcement powers are available to competent supervisory authorities in respect of potential and suspected violations of the GDPR, including extensive audit and inspection rights, and powers to order temporary or permanent bans on all or some processing of personal data carried out by noncompliant actors. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. There may be circumstances under which a failure to comply with GDPR, or the exercise of individual rights under the GDPR, would limit our ability to utilize clinical trial data collected on certain subjects. The GDPR will likely impose additional responsibility and liability in relation to our processing of personal data. This may be onerous and materially adversely affect our business, financial condition, results of operations and prospects.

A particular issue presented by the GDPR is the restriction on transfers of personal data from Europe to the United States and most other countries unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. One of the primary safeguards allowing U.S. companies to import personal data from Europe is the European Commission's Standard Contractual Clauses and we have relied on Standard Contractual Clauses to comply with the GDPR's restrictions on transfer of personal data out of Europe. However, in July 2020 the Court of Justice of the European Union, or CJEU, in a case known colloquially as "Schrems II" raised questions about whether the Standard Contractual Clauses can lawfully be used for personal data transfers from Europe to the United States or other third countries that are not the subject of an adequacy decision of the European Commission. While the CJEU upheld the adequacy of the Standard Contractual Clauses in principle in Schrems II, it made clear that reliance on those Clauses alone may not necessarily be sufficient in all circumstances. Use of the Standard Contractual Clauses must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular regarding applicable surveillance laws and relevant rights of individuals with respect to the transferred data. In the context of any given transfer, where the legal regime applicable in the destination country may or does conflict with the intended operation of the Standard Contractual Clauses and/or applicable European law, the decision in Schrems II and subsequent draft guidance from the European Data Protection Board, or EDPB, would require the parties to that transfer to implement certain supplementary technical, organizational and/or contractual measures to rely on the Standard Contractual Clauses as a compliant 'transfer mechanism.' However, the aforementioned draft guidance from the EDPB on such supplementary technical, organizational

and/or contractual measures appears to conclude that no combination of such measures could be sufficient to allow effective reliance on the Standard Contractual Clauses in the context of transfers of personal data 'in the clear' to recipients in countries where the power granted to public authorities to access the transferred data goes beyond that which is 'necessary and proportionate in a democratic society' – which may, following the CJEU's conclusions in Schrems II on relevant powers of United States public authorities and commentary in that draft EDPB guidance, include the United States in certain circumstances (e.g., where Section 702 of the US Foreign Intelligence Surveillance Act applies). At present, there are few, if any, viable alternatives to the Standard Contractual Clauses. As such, if we are unable to implement a valid solution for personal data transfers from Europe, including, we will face increased exposure to regulatory actions, substantial fines and injunctions against processing personal data from Europe. Inability to import personal data from Europe may also: restrict our activities in Europe; limit our ability to collaborate with partners as well as other service providers, contractors and other companies subject to European data protection laws; and require us to increase our data processing capabilities in Europe at significant expense. Restrictions on our ability to import personal data from Europe could therefore impact our clinical trial activities in Europe and limit our ability to collaborate with CROs and other third parties subject to European data protection laws. Additionally, other countries outside of Europe have enacted or are considering enacting similar cross-border data transfer restrictions and laws requiring local data residency, which could increase the cost and complexity of delivering our services and operating our business. The type of challenges we face in Europe will likely also arise in other jurisdictions that adopt laws similar in construction to the GDPR or regulatory frameworks of equivalent complexity.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in other jurisdictions, provide accurate information to the FDA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in government funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm and the curtailment or restructuring of our operations, any of which could have a negative impact on our business, financial condition, results of operations and prospects.

Our current or future acquisitions or strategic collaborations could increase our capital requirements, dilute our shareholders, cause us to incur debt or assume contingent liabilities and subject us to other risks.

We actively search for and continually evaluate various acquisition and strategic collaboration opportunities, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses, as deemed appropriate to carry out our business plan. Our collaborations, including any future acquisitions or strategic partnerships, may entail numerous risks, including:

- increased operating expenses and cash requirements;

- the assumption of additional indebtedness or contingent liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing drug programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or drugs sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, in connection with our current or future acquisitions or strategic partnerships, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable future acquisition opportunities, and this inability could impair our ability to grow or obtain access to technology or drugs that may be important to the development of our business.

Risks Related to Ownership of Our Common Shares

The market price of our common shares has been and may continue to be volatile and fluctuate substantially, and you could lose all or part of your investment.

The market price of our common shares has been and may continue to be highly volatile and could be subject to wide fluctuations in price in response to various factors, many of which are beyond our control. Since our initial public offering which occurred in May 2019, through March 29, 2023, the price of our common shares has ranged from $1.70 per share to $27.15 per share. The stock market in general and the market for biopharmaceutical and pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common shares at or above the price paid for the shares. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report on Form 10-K, the market price for our common shares may be influenced by the following:

- the commencement, enrollment or results of our planned or future clinical trials of etripamil and any future product candidates or those of our competitors;
- the success of competitive drugs or therapies;
- regulatory or legal developments in the United States and other countries;
- the success of competitive products or technologies;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to etripamil and any future product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;

- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- our inability to obtain or delays in obtaining adequate drug supply for any approved drug or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or shareholder litigation;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, including coverage and adequate reimbursement for any approved drug;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, political, and market conditions , including deteriorating market conditions due to investor concerns regarding inflation and Russian hostilities in Ukraine and overall fluctuations in the financial markets in the United States and abroad; and
- investors' general perception of us and our business.

These and other market and industry factors may cause the market price and demand for our common shares to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares at or above the price paid for the shares and may otherwise negatively affect the liquidity of our common shares. In addition, the stock market in general, and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time-consuming, and could divert our management's attention and our resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our common shares.

Geopolitical instability outside of the U.S. may adversely impact the U.S. and global economies.

At the end of 2022 and into 2023, tensions between the U.S. and Russia escalated when on February 24, 2022, Russia invaded Ukraine, Russia initiated a military conflict across Ukraine. In response, NATO has deployed additional military forces to Eastern Europe, including to Lithuania and Romania, and Australia, Britain, the European Union, Japan, Switzerland, Taiwan, the U.S. and other countries announced punishing sanctions against Russia. The Russo-Ukrainian conflict and any retaliatory measures taken by the U.S. and NATO could threaten global security and result in further regional conflict and otherwise have a lasting impact on regional and global economies. Although we do not have patients or clinical sites in Ukraine or Russia, we could experience an adverse affect our business and the price of our common stock.

Our common shares are thinly traded and our shareholders may be unable to sell their shares quickly or at market price.

Although we have had periods of high volume daily trading in our common shares, generally our shares are thinly traded. As a consequence of this lack of liquidity, the trading of relatively small quantities of shares by our shareholders may disproportionately influence the price of those shares in either direction. The price for our shares could, for example, decline significantly in the event that a large number of our common shares are sold on the market without commensurate demand, as compared to a seasoned issuer that could better absorb those sales without adverse impact on its share price.

Concentration of ownership of our common shares among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

Based upon our common shares outstanding as of December 31, 2022, our executive officers, directors and shareholders who owned more than 5% of our outstanding common shares, in the aggregate, beneficially owned shares representing 37.6% of our outstanding common shares. If our executive officers, directors and shareholders who owned more than 5% of our outstanding common shares acted together, they may be able to significantly influence all matters requiring shareholder approval, including the election and removal of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. The concentration of voting power and transfer restrictions could delay or prevent an acquisition of our company on terms that other shareholders may desire or result in the management of our company in ways with which other shareholders disagree.

If research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, our share price and trading volume could decline.

The trading market for our common shares will be influenced by the research and reports that industry or financial analysts publish about us or our business. Equity research analysts may discontinue research coverage of our common shares, and such lack of research coverage may adversely affect the market price of our common shares. We do not have any control over the analysts or the content and opinions included in their reports. The price of our shares could decline if one or more equity research analysts downgrade our shares or issue other unfavorable commentary or research about us. If one or more equity research analysts ceases coverage of us or fails to publish reports on us regularly, demand for our shares could decrease, which in turn could cause the trading price or trading volume of our common shares to decline.

Because we do not anticipate paying any cash dividends on our share capital in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

You should not rely on an investment in our common shares to provide dividend income. We have never declared or paid cash dividends on our share capital. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements or preferred equity may preclude us from paying dividends. As a result, capital appreciation, if any, of our common shares will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common shares.

We have broad discretion in the use of our cash and cash equivalents and may use them in ways in which you do not agree or in ways that do not increase the value of your investment.

Our management has broad discretion in the application of our cash and cash equivalents and could spend these funds in ways that do not improve our results of operations or enhance the value of our common shares. The failure by our management to apply these funds effectively could result in financial losses that could have a negative impact on our business, cause the price of our common shares to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents, in a manner that does not produce income or that loses value.

If we are a passive foreign investment company, there could be adverse U.S. federal income tax consequences to U.S. Holders (as defined below).

Based on the nature and composition of our income, assets, activities and market capitalization for our taxable year ending December 31, 2022, we believe that we may have been classified as a passive foreign investment company, or PFIC, for our taxable year ending December 31, 2022. Based on the expected nature and composition of our income and assets for our taxable year ending December 31, 2022, we expect that we may be classified as a PFIC for our taxable year ending December 31, 2022. If we are a PFIC for the current taxable year, or any subsequent taxable years, we intend to annually furnish U.S. Holders, upon request, a "PFIC Annual Information Statement," with the information required to allow U.S. Holders to make a "qualified electing fund" election, or "QEF Election" for United States federal income tax purposes. No assurances regarding our PFIC status can be provided for any past, current or future taxable years. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis and the applicable law is subject to varying interpretation. In particular, the characterization of our assets as active or passive may depend in part on our current and intended future business plans, which are subject to change. In addition, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our common shares from time to time, which may fluctuate considerably. As a result, our PFIC status may change from year to year. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by how, and how quickly, we spend the cash we raise in any offering.

If we are a PFIC, U.S. Holders may be subject to adverse U.S. federal income tax consequences, such as ineligibility for any preferential tax rates for individuals on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements under U.S. federal income tax laws and regulations.

A "U.S. Holder" is a holder of our common shares who, for U.S. federal income tax purposes, is: (i) an individual who is a citizen or resident of the United States; (ii) a corporation, or another entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia; (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or (iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S.Treasury Regulations.

If a U.S. Holder is treated as owning at least 10% of our common shares, such holder may be subject to adverse U.S. federal income tax consequences.

If a U.S. Holder is treated as owning (directly, indirectly or constructively) at least 10% of the value or voting power of our common shares, such U.S. Holder may be treated as a "United States shareholder" with respect to each "controlled foreign corporation" in our group (if any). Because our group includes at least one U.S. subsidiary (Milestone Pharmaceuticals USA Inc.), if we were to form or acquire any non-U.S. subsidiaries in the future, they may be treated as controlled foreign corporations. A United States shareholder of a controlled foreign corporation may be required to annually report and include in its U.S. taxable income its pro rata share of "Subpart F income," "global intangible low-taxed income" and investments in U.S. property by that controlled foreign corporation, regardless of whether that controlled foreign corporation, or we, make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. We cannot provide any assurances that we will assist investors in determining whether any non-U.S. subsidiaries that we may form or acquire in the future will be treated as controlled foreign corporations or whether any such investor would be treated as a United States shareholder with respect to any of such controlled foreign corporations. Further, we cannot provide any assurances that we will furnish to any investor information that may be necessary to comply with the reporting and tax paying obligations discussed above. Failure to comply with these reporting obligations may subject a U.S. Holder to significant monetary penalties and may extend the statute of limitations with respect to its U.S. federal income tax return for the year for which reporting was due. U.S. Holders should consult their tax advisors regarding the potential application of these rules to their investment in our common shares.

Future changes to tax laws could materially adversely affect our company and reduce net returns to our shareholders.

Our tax treatment is subject to the enactment of, or changes in, tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, including those related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices, could affect our financial position and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders, and increase the complexity, burden and cost of tax compliance.

For example, the Tax Act enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Act may affect us, and certain aspects of the Tax Act could be repealed or modified in future legislation. For example, the CARES Act modified certain provisions of the Tax Act. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the CARES Act or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense. We urge you to consult with your legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common shares.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, the Canadian Revenue Agency, the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the result could increase our anticipated effective tax rate.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common shares less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and

- not being required to hold a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We currently take advantage of some or all of these reporting exemptions and may continue to until we are no longer an EGC. We will remain an EGC until the earlier of (i) December 31, 2024, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.235 billion, (iii) the last day of the first fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our common shares that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (iv) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period. We cannot predict whether investors will find our common shares less attractive because we will rely on these exemptions. If some investors find our common shares less attractive as a result, there may be a less active trading market for our common shares and our share price may be more volatile.

In addition, under Section 107(b) of the JOBS Act, EGCs can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not EGCs.

We are incurring, and expect to continue to incur additional costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

As a public company, and particularly after we are no longer an EGC, we are incurring, and expect to continue to incur, significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and rules subsequently implemented by the SEC and The Nasdaq Stock Market LLC have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased, and will continue to increase, our legal and financial compliance costs and make some activities more time-consuming and costly.

While we remain an EGC, we are not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, pursuant to Section 404 of the Sarbanes Oxley Act, or Section 404, in the future we will be required to furnish an attestation on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404, we will be engaged in additional internal processes to document and evaluate our internal control over financial reporting, which will be both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, our independent registered public accounting firm may determine we have a material weakness or significant deficiency in our internal control over financial reporting once such firm begin its Section 404 reviews in the future, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our consolidated financial statements.

Because we are a Canadian company, it may be difficult to serve legal process or enforce judgments against us.

We are a domestic filer in the United States; however, we are incorporated and have our corporate headquarters in Canada. In addition, while many of our directors and officers reside in the United States, several of them reside outside of the United States. Accordingly, service of process upon us may be difficult to obtain within the United States. Furthermore, because substantially all of our assets are located outside the United States, any judgment obtained in the United States against us, including one predicated on the civil liability provisions of the U.S. federal securities laws, may not be collectible within the United States. Therefore, it may not be possible to enforce those actions against us.

In addition, it may be difficult to assert U.S. securities law claims in original actions instituted in Canada. Canadian courts may refuse to hear a claim based on an alleged violation of U.S. securities laws against us or these persons on the grounds that Canada is not the most appropriate forum in which to bring such a claim. Even if a Canadian court agrees to hear a claim, it may determine that Canadian law and not U.S. law is applicable to the claim. If U.S. law is found to be applicable, the content of applicable U.S. law must be proved as a fact, which can be a time-consuming and costly process. Certain matters of procedure will also be governed by Canadian law. Furthermore, it may not be possible to subject foreign persons or entities to the jurisdiction of the courts in Canada. Similarly, to the extent that our assets are located in Canada, investors may have difficulty collecting from us any judgments obtained in the U.S. courts and predicated on the civil liability provisions of U.S. securities provisions.

We are governed by the corporate laws of Québec, which in some cases have a different effect on shareholders than the corporate laws of Delaware.

We are governed by the Business Corporations Act (Québec), or the QBCA, and other relevant laws, which may affect the rights of shareholders differently than those of a company governed by the laws of a U.S. jurisdiction, and may, together with our charter documents, have the effect of delaying, deferring or discouraging another party from acquiring control of us by means of a tender offer, a proxy contest or otherwise, or may affect the price an acquiring party would be willing to offer in such an instance. The material differences between the QBCA and Delaware General Corporation Law, or the DGCL, that may have the greatest such effect include but are not limited to the following: (i) for material corporate transactions (such as mergers and amalgamations, other extraordinary corporate transactions or amendments to our articles), the QBCA generally requires a two-thirds majority vote by shareholders, whereas the DGCL generally only requires a majority vote; and (ii) under the QBCA, a holder of 5% or more of our common shares can requisition a special meeting of shareholders, whereas such right does not exist under the DGCL.

Our bylaws and certain Canadian legislation contain provisions that may have the effect of delaying or preventing certain change in control transactions or shareholder proposals.

Certain provisions of our bylaws and certain Canadian legislation, together or separately, could discourage or delay certain change in control transactions or shareholder proposals.

Our bylaws contain provisions that establish certain advance notice procedures for nomination of candidates for election as directors at shareholders' meetings. The BCA requires that any shareholder proposal that includes nominations for the election of directors must be signed by one or more holders of shares representing in the aggregate not less than 5% of the shares or 5% of the shares of a class or series of shares of the corporation entitled to vote at the meeting to which the proposal is to be presented.

The *Investment Canada Act* requires that a non-Canadian must file an application for review with the Minister responsible for the *Investment Canada Act* and obtain approval of the Minister prior to acquiring control of a "Canadian business" within the meaning of the *Investment Canada Act*, where prescribed financial thresholds are exceeded. Furthermore, limitations on the ability to acquire and hold our common shares may be imposed by the *Competition Act* (Canada). This legislation permits the Commissioner of Competition, or Commissioner, to review any acquisition or establishment, directly or indirectly, including through the acquisition of shares, of control over or of a significant interest in our company. Otherwise, there are no limitations either under the laws of Canada or Quebec, or in our articles on the rights of non-Canadians to hold or vote our common shares.

Any of these provisions may discourage a potential acquirer from proposing or completing a transaction that may have otherwise presented a premium to our shareholders.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our headquarters is currently located in Montréal (Québec), Canada and consists of 7,700 square feet of leased office space under a lease that expires in November 2025. We also have a U.S. subsidiary based in Charlotte, North Carolina. We believe that our facilities are adequate to meet our current needs and that additional space can be obtained on commercially reasonable terms as needed.

ITEM 3. LEGAL PROCEEDINGS.

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently a party to any material legal proceedings, and we are not aware of any pending or threatened legal proceeding against us that we believe could have an adverse effect on our business, operating results or financial condition.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

MARKET INFORMATION

Our common shares began trading on The Nasdaq Global Select Market on May 9, 2019. Our common shares trade under the symbol "MIST". Prior to the commencement of trading on the Nasdaq Global Select Market on May 9, 2019, there was no public market for our common shares.

HOLDERS OF RECORD

As of December 31, 2022, there were 15 holders of record of our common shares, including Cede & Co., a nominee for The Depository Trust Company, or DTC, which holds shares of our common shares on behalf of an indeterminate number of beneficial owners. All of the common shares held by brokerage firms, banks and other financial institutions as nominees for beneficial owners are deposited into participant accounts at DTC, and are considered to be held of record by Cede & Co. as one shareholder. Because many of our shares are held by brokers and other institutions on behalf of shareholders, we are unable to estimate the total number of shareholders represented by these record holders.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock and do not anticipate paying any cash dividends in the foreseeable future. Payment of cash dividends, if any, in the future will be at the discretion of our board of directors and will depend on then-existing conditions, including our financial condition, operating results, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

Recent Sales of Unregistered Securities

On February 15, 2022, we granted an inducement award in the form of an option to purchase 330,000 of our common shares to David Bharucha, M.D., Ph.D. in connection with his appointment as our Chief Medical Officer. The compensation committee of our board of directors granted the inducement award to Dr. Bharucha under the 2021 Inducement Plan that we adopted and the applicable award agreement thereunder, which terms are substantially similar to the terms of the Company's 2019 Equity Incentive Plan, as a material inducement to Dr. Bharucha's acceptance of employment in accordance with NASDAQ Listing Rule 5635(c)(4).

The inducement award was exempt from the registration requirements of the Securities Act by virtue of Section 4(a)(2) thereof and/or Regulation D promulgated thereunder. On March 24, 2022, we filed a registration statement on Form S-8 under the Securities Act to register all of the common shares subject to outstanding options and all common shares issuable pursuant to our equity compensation plans.

Purchase of Equity Securities by the Issuer and Affiliated Purchasers

None.

Securities Authorized for Issuance Under Equity Compensation Plans

Information about securities authorized for issuance under our equity compensation plan is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

ITEM 6. SELECTED FINANCIAL DATA.

Not Applicable.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS.

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements based upon current expectations that involve risks and uncertainties. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of various factors, including those discussed in "Risk Factors" and in other parts of this Annual Report on Form 10-K.

Company Overview

We are a biopharmaceutical company focused on the development and commercialization of innovative cardiovascular medicines. Our lead product candidate etripamil is a novel and, potent, calcium channel blocker that we designed as a rapid-onset nasal spray to be self-administered by patients. We are developing etripamil for the treatment of specific arrhythmias with a lead indication to treat paroxysmal supraventricular tachycardia, or PSVT, and a subsequent indication to treat atrial fibrillation with rapid ventricular rate, or AFib-RVR.

Etripamil - Pivotal Clinical Program in PSVT

PSVT is a rapid heart rate condition characterized by episodes of supraventricular tachycardia, or SVT, that start and stop without warning. Episodes of SVT are often experienced by patients with symptoms including palpitations, sweating, chest pressure or pain, shortness of breath, sudden onset of fatigue, lightheadedness or dizziness, fainting and anxiety. Calcium channel blockers have long been approved for the treatment of PSVT as well as other cardiac conditions. Calcium channel blockers available in oral form are frequently used prophylactically to control the frequency and duration of future episodes of SVT. For treatment of episodes of SVT, approved calcium channel blockers are administered intravenously under medical supervision, usually in the emergency department. The combination of convenient nasal-spray delivery, rapid-onset and short duration of action of etripamil has the potential to shift the current treatment paradigm for episodes of SVT away from the burdensome and costly emergency department setting. If approved, we believe that etripamil will be the first self-administered therapy for the rapid termination of episodes of SVT wherever and whenever they occur.

On October 17, 2022, we announced positive and statistically significant topline efficacy and safety data from the Phase 3 RAPID clinical trial of etripamil in patients with PSVT. These results were further presented shortly thereafter, on November 7, 2022, as a Late-Breaking Clinical Trial at the American Heart Association Scientific Meetings (Chicago, IL). RAPID, our multi-center, randomized, double-blind, placebo-controlled, event-driven Phase 3 trial, enrolled 706 patients across clinical sites in North America and Europe. Patients were randomized 1:1 to a regimen of self-administering a first dose etripamil nasal spray, with a repeat dose 10 minutes later if symptoms persisted, or a matching placebo regimen. Self-administration was prompted by a patient's customary symptoms and was performed in the at-home setting without medical supervision. The RAPID trial achieved its primary endpoint, with patients taking the etripamil regimen demonstrating a highly statistically significant and clinically meaningful difference in time to SVT conversion as compared to placebo. A Kaplan Meier analysis demonstrated a significantly greater proportion of patients who took etripamil converted within thirty minutes compared to placebo (64.3% vs. 31.2%; hazard ratio, or HR, 2.62; 95% CI 1.66, 4.15; $p<0.001$). By 90 minutes post-study drug administration, 80.6% of etripamil patients converted versus 60.7% of placebo patients (HR = 1.93; 95% CI 1.349, 2.752; $p<0.001$) and statistical significance was maintained throughout the 5-hour observation window. Statistically significant reductions in time to conversion in patients who took etripamil were evident early and persisted throughout the observation window of the study compared to placebo. The median time to conversion for patients in RAPID who self-administered etripamil was 17.2 minutes compared to 53.3 minutes for patients on placebo. The safety and tolerability data from the RAPID trial continue to support the potential self-administration use of etripamil, with findings consistent with those observed in prior trials. The most common randomized-treatment emergent adverse events, or RTEAEs, adverse events, or AEs, which occurred within 24 hours of etripamil administration, were related to the nasal local administration site. Overall, the majority of RTEAEs were reported as mild (68%) or moderate (31%). There were no serious AEs related to etripamil.

The use of additional medical interventions and emergency department utilization were important secondary measures of efficacy for both the RAPID and NODE-301 studies, although with the understanding that neither study was individually powered to expect statistical differences. In a pre-planned analysis across both studies, patients who self-administered etripamil sought additional medical interventions 43% less frequently (15% vs. 25%; p=0.013) and had 39% fewer emergency department visits (14% vs. 22%; p=0.035) than patients in the placebo arm.

NODE-303 is a Phase 3, multi-center, open-label safety trial, evaluating primarily the safety of etripamil when self-administered without medical supervision over multiple, separate SVT episodes. After consultation with the regulatory authorities, it was concluded that the test dose procedure was an unnecessary step for the self-administration of etripamil and it was removed from the requirements of the NODE-303 safety study. The NODE-303 trial was initiated with an etripamil 70 mg single-dose regimen and the 70 mg optional repeat-dose regimen was introduced into the trial starting in the second half of 2021 following FDA acceptance of the protocol amendment. The trial was sized in order to add to the safety data from the remainder of the development program, including those data already obtained from the RAPID, NODE-301 and NODE-302 trials, in order to fulfill the safety and exposure dataset needed for NDA filing. Following the results from the RAPID study, initially obtained in October 2022, and the assessment of the total exposures to etripamil in the development program to date, we believe we have the safety dataset needed for review of the NDA for PSVT and have closed the NODE-303 study.

We are conducting patient access programs to provide further access to etripamil to patients who have participated in the clinical development registration trials to treat their future SVT episodes. These programs are tailored to meet the regulatory requirements in the territories in which the clinical sites are located.

The NODE-301 trial is a placebo-controlled Phase 3 safety and efficacy trial and the first trial ever conducted to treat attacks of PSVT in the at-home setting. NODE-301 enrolled 431 patients across 65 sites in the United States and Canada. Although the study did not meet its primary endpoint of time to conversion of SVT to sinus rhythm compared to placebo over the five-hour period following study drug administration in which patients wore a cardiac monitor, both prespecified and post hoc analyses at earlier time periods, namely at 30 minutes, showed significant treatment effects in favor of etripamil. For example, in a post hoc analysis of the NODE-301 data, 54% of etripamil patients vs. 35% of placebo patients converted within 30 minutes (HR 1.87, p=0.02). The safety and tolerability data from the NODE-301 trial support the potential self-administration use of etripamil, with the most common randomized treatment emergent adverse events, or RTEAEs, adverse events, or AEs, which occurred within 24 hours of etripamil administration, being related to the nasal local administration site. Overall, the majority of RTEAEs were reported as mild (85%) to moderate (15%). There were no serious AEs related to etripamil. After reviewing the data from NODE-301 with the FDA in July 2020, the Agency indicated that an analysis period shorter than 5 hours would be appropriate to measure the efficacy of etripamil. The FDA indicated that two trials, the RAPID and NODE-301 trials could potentially fulfill the efficacy requirement for our planned NDA for etripamil in patients with PSVT, both using time to conversion over the first 30 minutes with a target p-value of less than 0.05 as the primary endpoint.

AFIB RVR Phase 2 Proof of Concept Trial

The Phase 2, double-blind, placebo-controlled, proof-of-concept study, Reduction of Ventricular Rate in Patients with Atrial Fibrillation (ReVeRA), in patients with atrial fibrillation with rapid ventricular response (AFib/RVR), is being conducted in Canada and the Netherlands in collaboration with the Montreal Heart Institute, the WCN network, and other research centers. The ReVeRA study is expected to enroll approximately 50 patients randomized 1:1 to receive either 70 mg of etripamil nasal spray or placebo to patients presenting with symptomatic AFib/RVR. The primary endpoint will assess reduction in ventricular rate, with key secondary endpoints including the time to achieve the maximum reduction in rate and the duration of the effect. The trial is being conducted in the emergency department setting under medical supervision.

Operations Overview

Since the commencement of our operations in 2003, we have devoted substantially all of our resources to performing research and development activities in support of our product development efforts, hiring personnel, raising capital to support and expand such activities, providing general and administrative support for these operations and, more recently preparing for commercialization. We operate our business using a significant outsourcing model. As such, our team is composed of a relatively smaller core of employees who direct a significantly larger number of team members who are outsourced in the forms of vendors and consultants to enable execution of our operational plans. We do not currently have any products approved for sale, and we continue to incur significant research and development and general administrative expenses related to our operations.

Since inception, we have incurred significant operating losses. For the years ended December 31, 2022 and 2021, we recorded net losses of $58.4 million and $42.9 million, respectively. As of December 31, 2022, we had an accumulated deficit of $266.3 million. We expect to continue to incur significant losses for the foreseeable future. We anticipate that a substantial portion of our capital resources and efforts in the foreseeable future will be focused on completing the necessary development activities required for obtaining regulatory approval and preparing for potential commercialization of our product candidates. We had $7.6 million of cash and cash equivalents and $56.9 million of short-term investments at December 31, 2022.

We expect to continue to incur significant expenses and increasing operating losses for at least the next several years. Our net losses may fluctuate significantly from period to period, depending on the timing of our planned clinical trials and expenditures on other research and development activities. We expect our expenses will increase substantially over time as we:

- continue our ongoing and planned development of etripamil, including our Phase 3 clinical trials of etripamil for the treatment of PSVT and our Phase 2 clinical trial of etripamil for the treatment of AFib-RVR;
- seek marketing approvals for etripamil for the treatment of PSVT, AFib-RVR and other cardiovascular indications;
- establish a sales, marketing, manufacturing and distribution capability, either directly or indirectly through third parties, to commercialize etripamil or any future product candidate for which we may obtain marketing approval;
- build a portfolio of product candidates through development, or the acquisition or in-license of drugs, product candidates or technologies;
- initiate preclinical studies and clinical trials for etripamil for any additional indications we may pursue, including the clinical trials for the treatment of atrial fibrillation and rapid ventricular rate as well as other areas of unmet medical need, and for any additional product candidates that we may pursue in the future;
- maintain, protect and expand our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- incur additional legal, accounting, insurance and other expenses associated with operating as a public company.

Recent Developments

Board Appointment

On March 21, 2023, the board of directors voted to elect Seth H.Z. Fischer to the Board, effective as of March 21, 2023. Mr. Fischer brings to the Board over 40 years of experience in the pharmaceutical and medical device industry, including 29 years in various leadership roles at Johnson & Johnson. Mr. Fischer currently serves as a member of the Board of Directors of Agile Therapeutics, Inc. (AGRX), Marinus Pharmaceuticals, Inc. (MRNS), Spectrum Pharmaceuticals, Inc. (SPPI), and Esperion Therapeutics, Inc. (ESPR).

Exchange Agreement

On March 22, 2023, we entered into an exchange agreement, or the Exchange Agreement, with entities affiliated with RTW, or the Exchanging Stockholders, pursuant to which the Company exchanged an aggregate of 1,059,000 shares of the Company's common shares owned by the Exchanging Stockholders for pre-funded warrants, or the Exchange Warrants, to purchase an aggregate of 1,059,000 common shares, with an exercise price of $0.001 per share and no expiration date. The Exchange Warrants are exercisable immediately. A holder of the Exchange Warrants (together with its affiliates and other attribution parties) may not exercise any portion of an Exchange Warrant to the extent that immediately prior to or after giving effect to such exercise the holder would beneficially own more than 9.99% of the Company's outstanding common shares immediately after exercise, which percentage may be increased or decreased to any other percentage specified not in excess of 9.99% at the holder's election upon 61 days' notice to the Company subject to the terms of the Exchange Warrants.

Strategic Financing Transactions

On March 27, 2023, we entered into a purchase and sale agreement, or the Royalty Purchase Agreement, and a note purchase agreement, or the Note Purchase Agreement, with RTW and certain of its affiliates.

Pursuant to the Royalty Purchase Agreement, RTW agreed to purchase, following the U.S. Food and Drug Administration approval of etripamil (subject to certain conditions), in exchange for a purchase price of $75.0 million, the right to receive a tiered quarterly royalty payments, or the royalty interest, on the annual net product sales of etripamil in the United States in an amount equal to: (i) 7%, or the Initial Tier Royalty, of annual net sales up to $500 million, (ii) 4% of annual net sales greater than $500 million and less than or equal to $800 million, and (iii) 1% of annual net sales greater than $800 million. If certain revenue thresholds for aggregate annual net sales in the United States are not met, the Initial Tier Royalty will increase to 9.5% beginning on January 1 of the following calendar year until a subsequent sales threshold is attained, at which time the Initial Tier Royalty would revert back to 7%.

The Royalty Purchase Agreement contains various representations and warranties, covenants, indemnification obligations and other provisions customary for transactions of this nature, including the grant of a back-up security interests in the purchased royalties and certain assets related to etripamil and restrictions on the incurrence of additional indebtedness.

Pursuant to the Note Purchase Agreement, we will issue and sell $50 million principal amount of 6.0% Convertible Senior Notes due 2029, or the 2029 Convertible Notes, to the holders, which is expected to close on March 29, 2023.

The 2029 Convertible Notes will be our senior secured obligations and will be guaranteed on a senior secured basis by our wholly owned subsidiary, Milestone Pharmaceuticals USA, Inc. Interest at the annual rate of 6.0% is payable quarterly in cash or, at our option, payable in kind for the first three years. The maturity date for the 2029 Convertible Notes will be March 31, 2029, or the Maturity Date. The obligations under the 2029 Convertible Notes will be secured by substantially all of our and our subsidiary guarantor's assets.

Each $1,000 of principal of the 2029 Convertible Notes (including any interest added thereto as payment in kind) is convertible into 191.0548 shares of our common shares, equivalent to an initial conversion price of approximately $5.23 per share, subject to customary anti-dilution adjustments. In addition, following a notice of redemption or certain corporate events that occur prior to the Maturity Date, we will, in certain circumstances, increase the conversion rate for a Holder who elects to convert its 2029 Convertible Notes in connection with such notice of redemption or corporate event.

Subject to specified conditions, on or after March 27, 2027, the 2029 Convertible Notes are redeemable by us if the closing sale price of the common shares exceeds 150% of the conversion price then in effect for at least 20 trading days (whether or not consecutive), including the trading day immediately preceding the date on which we provide notice of redemption, during any 30 consecutive trading day period ending on, and including, the trading day immediately preceding the date on which we provide notice of redemption, at a redemption price equal to 100% of the principal amount of the 2029 Convertible Notes to be redeemed, plus accrued and unpaid interest to, but excluding, the redemption date.

The Note Purchase Agreement contains customary terms and covenants, including negative covenants, such as limitations on indebtedness, liens, disposition of royalty interest and mergers. The Note Purchase Agreement also contains customary events of default, including defaults related to payment compliance, material inaccuracy of representations and warranties, covenant compliance, bankruptcy and insolvency proceedings, cross defaults to certain other agreements, judgment default and certain clinical trial failures.

The descriptions of the Royalty Purchase Agreement and the Note Purchase Agreement are not complete and are qualified in its entirety by reference to the complete text of the Royalty Purchase Agreement and the Note Purchase Agreement, which will be filed as an exhibit to the Company's Quarterly Report on Form 10-Q for the quarter ending March 31, 2023.

The Macroeconomic Climate

The recent trends towards rising inflation may also materially adversely affect our business and corresponding financial position and cash flows. Inflationary factors, interest rates and overhead costs may adversely affect our operating results. Rising interest and inflation rates also present a recent challenge impacting the U.S. economy and could make it more difficult for us to obtain traditional financing on acceptable terms, if at all, in the future. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may experience increases in the near future (especially if inflation rates continue to rise) on our operating costs, including our labor, due to supply chain constraints, consequences associated with COVID-19 and the Russia-Ukraine war, and employee availability and wage increases, which may result in additional stress on our working capital resources.

Components of Results of Operations

Revenues

We have not generated any revenues from product sales to date and we do not expect to generate revenues from product sales in the near future. Our revenues of $5 million for the year ended December 31, 2022 compared to $15 million for the year ended December 31, 2021 are from the license agreement with Ji Xing and are comprised of upfront and milestone payments. For additional information about our Revenue, see "Note 2— Summary of Significant Accounting Policies, and Note 3 - Revenue."

Research and Development Expenses

Research and development expenses consist primarily of salaries and fees paid to external service providers and also include personnel costs, including share-based compensation expense and other related compensation expenses. We expense research and development costs in the periods in which they are incurred. Costs for certain development activities are recognized based on an evaluation of the progress to completion of specific tasks using information and data provided to us by our vendors, collaborators and third-party service providers.

To date, substantially all of our research and development expenses have been related to the preclinical and clinical development of etripamil. As we advance etripamil or other product candidates for other indications, we expect to allocate our direct external research and development costs across each of the indications or product candidates. Further, we expect our research and development costs to increase for the development of etripamil in atrial fibrillation with rapid ventricular rate, and we expect our research and development expenses related to the development of etripamil for PSVT decrease as a percentage of our total research and development expenses.

The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming and is subject to uncertainties and delays. As a result of the uncertainties discussed above, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of our product candidates, if at all.

We recognize the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits. General and administrative expenses include personnel and related compensation costs, expenses for outside professional services, lease expense, insurance expense and other general administrative expenses. Personnel costs consist of salaries, bonuses, benefits, related payroll taxes and share-based compensation. Outside professional services consist of legal, accounting and audit services and other consulting fees.

We expect to continue to incur expenses as a public company, including expenses related to compliance with the rules and regulations of the Securities and Exchange Commission, or SEC, and those of any national securities exchange on which our securities are traded, additional insurance expenses, investor relations activities, and other administrative and professional services.

Commercial Expenses

Commercial expenses consist primarily of personnel and related compensation costs, market and health economic research, and market development activities for PSVT and, to a lesser extent, AFib-RVR. The focus of these expenses is three-fold: first, we want to leverage rigorous primary and secondary research to fully understand our target disease states from the perspective of the patient, healthcare provider, and payer; second, we want to understand and document the burden of disease posed by PSVT and AFib-RVR from an epidemiology, healthcare resource use, and cost perspective; and third, we want to engage our target patient, physician, and payer stakeholders with evidence-based and compliant educational materials that serve to increase the awareness and understanding of the impact of PSVT and AFib-RVR on patients and the overall healthcare system.

We anticipate our commercial expenses will increase substantially as we invest in the infrastructure, personnel, and operational expenses required to launch our first product in the United States, if approved.

Interest Income

Interest income primarily consists of interest income from our cash equivalents and short-term investments.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

	Year ended December 31,			
(in thousands)	**2022**	**2021**	**$ Change**	**% Change**
Revenue	$ 5,000	$ 15,000	$ (10,000)	(66.7)%
Operating expenses				
Research and development, net of tax credits	39,829	38,671	1,158	3.0%
General and administrative	15,718	12,399	3,319	26.8%
Commercial	9,095	7,003	2,092	29.9%
Total operating expenses	64,642	58,073	6,569	11.3%
Loss from operations	(59,642)	(43,073)	(16,569)	38.5%
Interest income, net	1,254	220	1,034	470.0%
Net loss	(58,388)	(42,853)	(15,535)	36.3%

Revenue

We generated revenue of $5.0 million for the year ended December 31, 2022 compared to $15.0 million for the year ended December 31, 2021. This revenue is from the license agreement with Ji Xing and is comprised of upfront and milestone payments.

Research and Development Expenses

The following table shows our research and development expenses by type of activity for the periods indicated.

	Year ended December 31,			
(in thousands)	**2022**	**2021**	**$ Change**	**% Change**
Clinical	$ 35,264	$ 30,984	$ 4,280	13.8%
Drug manufacturing and formulation	3,607	5,691	(2,084)	(36.6)%
Regulatory and other costs	1,414	2,454	(1,040)	(42.4)%
Less: R&D tax credits	(456)	(458)	2	(0.4)%
Total R&D expenses	$ 39,829	$ 38,671	$ 1,158	3.0%

Research and development expenses increased by $1.2 million, or 3% for the year ended December 31, 2022 compared to the year ended December 31, 2021. Clinical expenses increased by $4.3 million mainly due to an increase of $4.2 million in clinical consulting fees and CRO costs due to the conduct of the RAPID Phase 3 trial. This increase was partially offset by a $2.1 million decrease in drug manufacturing and formulation mainly due to a decrease of $2 million in drug manufacturing and formulation consulting and CMO cost and further offset by a $1.0 million decrease in regulatory costs mainly due to $0.8 million decrease in regulatory consulting and employee related expenses.

General and Administrative

General and administrative expenses increased by $3.3 million, or 26.8% for the year ended December 31, 2022 compared to the year ended December 31, 2021. The primary contributors to the increase was due to the increase of personnel related costs and an increase in professional and consulting costs. Personnel related costs increased by $2.3 million, including a $1.6 million increase in non-cash compensation, as a result of hiring more full-time employees. Further, professional and consulting fees also increased by $1 million to meet the needs of the our growing operations.

Commercial

Commercial expenses increased by $2.1 million, or 29.9%, for the year ended December 31, 2022, compared to the same period in the December 31, 2021. The increase is due to marketing and personnel related costs, which includes an increase in non-cash compensation costs related to share-based compensation expense. This increase is a result of additional personnel and professional costs required to expand operations in anticipation of the potential market approval and commercialization.

Interest Income, net

Interest income, net, was $1.3 million and $0.2 million for the year ended December 31, 2022 and 2021, respectively. The increase in interest income was due to higher interest rates earned on investments in 2022 when compared to 2021.

Liquidity and Capital Resources

Sources of Liquidity

We have incurred operating losses and experienced negative operating cash flows since our inception, and we anticipate continuing to incur losses for at least the next several years. As of December 31, 2022, we had cash and cash equivalents of $7.6 million, short-term investments of $56.9 million and an accumulated deficit of $266.3 million.

On May 15, 2021, pursuant to the License Agreement, we and affiliates of RTW Investments, LP, (RTW), or the Purchasers, entered into a securities purchase agreement pursuant to which we issued to the Purchasers, in a private placement, pre-funded warrants to purchase up to an aggregate of 910,746 of our common shares at a purchase price of $5.48 per pre-funded warrant, or the Private Placement. The gross proceeds to us from the Private Placement, excluding proceeds from the exercise price of the warrants, were approximately $5.0 million.

On July 29, 2020, we entered into an Open Market Sale Agreement℠, or the Sales Agreement, with Jefferies LLC, or Jefferies, with respect to an at-the-market offering program, or the ATM Program, under which we may issue and sell our common shares having an aggregate offering price of up to $50 million through Jefferies as our sales agent or principal. The common shares to be sold under the Sales Agreement, if any, will be offered and sold pursuant to our shelf registration statement on Form S-3 (File No. 333-239318), which was declared effective by the Securities and Exchange Commission on July 6, 2020. During the year ended December 31, 2022, we issued 361,236 shares under the Sales Agreement, resulting in net proceeds of $2.6 million (net of issuance costs of $0.1 million).

We expect that our current operating plan, existing cash and cash equivalents and the $50 million in funding contained within the Strategic Financing Agreement signed on March 27, 2023 to be sufficient to fund our operations for at least the next 12 months and determined that there are no events or conditions that may cast substantial doubt on our ability to continue as a going concern for at least the next 12 months from the date of this filing.

Funding Requirements

We use our cash primarily to fund research and development expenditures. We expect our research and development expenses to increase as we continue the development of etripamil and prepare to pursue regulatory approval. We expect to incur an increase in general and administrative expenses, and an increase in expenses related to commercial activities in 2023 as we focus our efforts on the clinical pathway and potential commercialization of etripamil. We expect to incur increasing operating losses for the foreseeable future as we continue the clinical development of our product candidate. At this time, due to the inherently unpredictable nature of clinical development, we cannot reasonably estimate the costs we will incur and the timelines that will be required to complete development, obtain marketing approval, and commercialize etripamil or any future product candidates, if at all. For the same reasons, we are also unable to predict when, if ever, we will generate revenue from product sales or whether, or when, if ever, we may achieve profitability. Clinical and preclinical development timelines, the probability of success, and development costs can differ materially from expectations.

In addition, we have exclusive development and commercialization rights for etripamil for all indications that we may pursue and as such have the potential to license development and or commercialization rights for etripamil to a potential partner in regions outside of Greater China. We plan to establish commercialization and marketing capabilities using a direct sales force to commercialize etripamil in the United States. Outside of the United States, we are considering commercialization strategies that may include collaborations with other companies.

For other new product candidates, our efforts are focused on licensing development and/or commercialization rights from potential partners. In the case of either in-licensing or out-licensing, we cannot forecast when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development and commercialization plans and capital requirements.

The timing and amount of our operating expenditures will depend largely on:

- the timing, progress and results of our ongoing and planned clinical trials and other development activities of etripamil in PSVT, AFib-RVR and in other cardiovascular indications;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of etripamil for additional indications or any future product candidates that we may pursue;
- our ability to establish additional collaborations on favorable terms, if at all;

- the ability of vendors and third-party service providers to accurately forecast expenses and deliver on expectations;
- the costs, timing and outcome of regulatory review of etripamil and any future product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for etripamil and any future product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of etripamil and any future product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims; and
- the extent to which we acquire or in-license other product candidates and technologies.

Until such time, if ever, as we can generate substantial revenue from product sales, we expect to fund our operations and capital funding needs through equity and/or debt financing. We may also consider entering into collaboration arrangements or selectively partnering for clinical development and commercialization. The sale of additional equity would result in additional dilution to our shareholders. The incurrence of debt financing would result in debt service obligations and the instruments governing such debt could provide for operating and financing covenants that restrict our operations or our ability to incur additional indebtedness or pay dividends, among other items. If we are not able to secure adequate additional funding, we may be forced to make reductions in spending, extend payment terms with suppliers, liquidate assets where possible, and/or suspend or curtail planned programs. Any of these actions could materially and adversely affect our business, financial condition and results of operations.

Cash Flows

The following table summarizes our cash flows for the periods indicated:

	Year ended December 31,			
(in thousands)	**2022**	**2021**	**$ Change**	**% Change**
Net cash (used in) provided by:				
Operating activities	$ (52,469)	$ (33,224)	(19,245)	57.9%
Investing activities	(57,124)	70,000	(127,124)	(181.6)%
Financing activities	3,088	5,055	(1,967)	(38.9)%
Net increase (decrease) in cash and cash equivalents during the period	$ (106,505)	$ 41,831	(148,336)	

Operating Activities

Net cash used in operating activities during the year ended December 31, 2022 was $52.5 million, which consisted of a net loss of $58.4 million and a net cash decrease of $3.3 million in our operating assets and liabilities, in addition to non-cash charges of $9.2 million primarily related to share-based compensation.

Net cash used in operating activities during the year ended December 31, 2021 was $33.2 million, which consisted of a net loss of $42.9 million and a net change of $2.6 million in our operating assets and liabilities, in addition to non-cash charges of $7.4 million related to share-based compensation and depreciation expenses.

Investing Activities

In the year ended December 31, 2022, we redeemed $29.0 million of short-term investments and we acquired $85.9 million of short-term investments, in addition we acquired $0.3 million in property and equipment. These short-term investment acquisitions resulted in a growth of $56.9 million in short term investments for the year ended December 31, 2022. In the year ended December 31, 2021, we redeemed $85.0 million of short-term investments and we acquired $15.0 million of short-term investments

Financing Activities

In the year ended December 31, 2022, our financing activities provided cash of $3.1 million from the issuance of common shares under the Sales Agreement for proceeds of $2.6 million (net of issuance costs of $0.1 million) and a de minimis amount of proceeds from the exercise of share options and warrants. In the year ended December 31, 2021, our financing activities provided $5.0 million, consisting of net proceeds from the Private Placement and a de minimis amount of proceeds from the exercise of share options.

Contractual Obligations

We enter into contracts in the normal course of business with clinical research organizations, or CROs, contract manufacturing organizations, or CMOs, and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. These contracts are generally cancelable at our option with various notice requirements as defined in the contract. Payments due upon cancellation consist of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to and through the date of cancellation. These payments are not included as the amount and timing of these payments are not known.

Critical Accounting Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements as at December 31, 2022, which have been prepared in accordance with United States generally accepted accounting principles, or U.S. GAAP and on a basis consistent with those accounting principles followed by us. The preparation of these consolidated financial statements requires our management to make judgments and estimates that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported revenue generated and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Significant estimates and judgments include, but are not limited to:

- Estimates of the percentage of work completed of the total work over the life of the individual trial in accordance with agreements established with CROs, CMOs and clinical trial sites which in turn impact the research & development expenses.

- Estimate of the grant date fair value share options granted to employees, consultants and direct, and the resulting share-based compensation expense, using the Black-Scholes option-pricing model.

Accordingly, actual results may differ from these judgments and estimates under different assumptions or conditions and any such differences may be material. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

a) Research & Development Expenses — Accruals

Research and development costs are charged against income in the period of expenditure. Our research and development costs consist primarily of salaries and fees paid to CROs and to CMO.

Clinical trial expenses include direct costs associated with CROs, direct CMO costs for the formulation and packaging of clinical trial material, as well as investigator and patient-related costs at sites at which our trials are being conducted. Direct costs associated with our CROs and CMOs are generally payable on a time-and-materials basis, or when milestones are achieved. The invoicing from clinical trial sites can lag several months. We record expenses for our clinical trial activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the individual trial in accordance with agreements established with CROs and clinical trial sites. We determine the estimates through discussions with internal clinical personnel, CROs and CMOs as to the progress or stage of completion of trials or services and the agreed-upon fee to be paid for such services based on facts and circumstances known to us as of each consolidated balance sheet date. The actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan. If the actual timing of the performance of services of the level of effort varies from the estimate, we will adjust the accrual accordingly. Adjustments to prior period estimates have not been material. We recognize the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits and as a reduction of income taxes for investment tax credits that can only be claimed against income taxes payable when there is reasonable assurance that the claim will be recovered.

b) Share-Based Compensation

We recognize compensation costs related to share options granted to employees, consultants and directors based on the estimated fair value of the awards on the date of grant. We estimate the grant date fair value, and the resulting share-based compensation expense, using the Black-Scholes option-pricing model. This Black-Scholes option pricing model uses various inputs to measure fair value, including estimated fair value of our underlying common shares at the grant date, expected term, estimated volatility, risk-free interest rate and expected dividend yields of our common shares. The estimated volatility creates a critical estimate because we have not been a public company long enough to demonstrate our own historical volatility. The grant date fair value of the share-based awards is recognized on a straight-line basis over the requisite service periods, which are generally the vesting period of the respective awards. Forfeitures are accounted for as they occur.

The following table summarizes, by grant date, the number of underlying common shares and the associated per-share exercise price, which was the fair value per share as determined by our board of directors on the applicable grant date, for share options granted during the years ended December 31, 2022 and 2021:

	Number of Common Shares Subject to Options Granted	Exercise Price Per Common Share	Estimated Fair Value per Common Share at Grant Date	Estimated Per-Share Fair Value of Options
March 1, 2021	70,000	$ 7.510	$ 7.510	$ 5.672
March 24, 2021	1,793,950	$ 6.260	$ 6.260	$ 4.758
April 26, 2021	11,300	$ 5.910	$ 5.910	$ 4.490
June 14, 2021	180,000	$ 5.540	$ 5.540	$ 3.958
August 30, 2021	7,300	$ 6.070	$ 6.070	$ 4.606
September 13, 2021	2,650	$ 5.650	$ 5.650	$ 4.287
October 1, 2021	8,050	$ 5.640	$ 5.640	$ 4.282
November 1, 2021	64,000	$ 5.700	$ 5.700	$ 4.314
January 4, 2022	7,300	$ 7.45	$ 7.450	$ 5.694
February 15, 2022	330,000	$ 6.47	$ 6.470	$ 4.875
March 21, 2022	1,388,400	$ 5.46	$ 5.460	$ 4.118
April 1, 2022	65,000	$ 6.85	$ 6.850	$ 5.172
April 11, 2022	36,000	$ 6.93	$ 6.930	$ 5.246
May 16, 2022	92,000	$ 5.48	$ 5.480	$ 4.178
July 5, 2022	150,000	$ 6.07	$ 6.070	$ 4.491
July 18, 2022	17,000	$ 6.45	$ 6.450	$ 4.979
August 1, 2022	2,000	$ 7.3	$ 7.300	$ 5.606
August 8, 2022	2,000	$ 6.76	$ 6.760	$ 5.204
August 15, 2022	100,000	$ 7.1	$ 7.100	$ 5.486
August 29, 2022	70,000	$ 8.2	$ 8.200	$ 6.350
September 8, 2022	22,000	$ 8.53	$ 8.530	$ 6.609
November 2, 2022	20,000	$ 5.03	$ 5.030	$ 4.693
November 8, 2022	12,000	$ 4.22	$ 4.220	$ 3.936

The intrinsic value of all outstanding options as of December 31, 2022 was $3.8 million, based on the fair value of our common shares of $3.96 per share at December 31, 2022.

Recent Accounting Pronouncements

Refer to Note 2, “Summary of Significant Accounting Policies,” in the accompanying notes to our consolidated financial statements for a discussion of recent accounting pronouncements.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012 permits an “emerging growth company” such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to “opt out” of this provision and, as a result, we comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risks in the ordinary course of our business. These risks primarily relate to interest rate risks. For the year ended December 31, 2022, we had cash and cash equivalents and short-term investments of $7.6 million and $56.9 million, respectively. For the year ended December 31, 2021 we had cash and cash equivalents of $114.1 million. These cash and cash equivalents and short-term investments consist primarily of bank deposits and guaranteed investment certificates. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio, we do not believe an immediate 10% increase or decrease in interest rates would have a material effect on the fair market value of our portfolio, and accordingly we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

We undertake certain transactions in Canadian dollars and as such are subject to risk due to fluctuations in exchange rates. Canadian dollar denominated payables are paid at the converted rate as due. We do not use derivative instruments to hedge exposure to foreign exchange rate risk due to the low volume of transactions denominated in foreign currencies. At December 31, 2022 and 2021, our net monetary exposure denominated in Canadian dollars was $0.1 million and $1.1 million, respectively.

Our operating results and financial position are reported in U.S. dollars in our financial statements. The fluctuation of the Canadian dollar in relation to the U.S. dollar might, consequently, have an impact upon our loss and may also affect the value of our assets and the amount of shareholders' equity. We do not believe that inflation and changing prices had a significant impact on our results of operations for any periods presented herein.

ITEM 8. FINANCIAL STATEMENTS

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors of Milestone Pharmaceuticals Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Milestone Pharmaceuticals Inc. and its subsidiary (together, the Company) as of December 31, 2022 and 2021, and the related consolidated statements of loss, shareholders' equity and of cash flows for the years then ended, including the related notes (collectively referred to as the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for the years then ended in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/PricewaterhouseCoopers LLP
Montreal, Canada
March 29, 2023

We have served as the Company's auditor since 2016

Milestone Pharmaceuticals Inc.
Consolidated Balance Sheets
(in thousands of US dollars, except share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets		
Cash and cash equivalents	$ 7,636	$ 114,141
Short-term investments	56,949	—
Research and development tax credits receivable	331	356
Prepaid expenses	6,005	4,299
Other receivables	882	127
Total current assets	71,803	118,923
Operating lease assets	2,423	711
Property and equipment	257	215
Total assets	$ 74,483	$ 119,849
Liabilities, and Shareholders' Equity		
Current liabilities		
Accounts payable and accrued liabilities	$ 5,644	$ 6,551
Operating lease liabilities	495	224
Total current liabilities	6,139	6,775
Operating lease liabilities (net of current portion)	1,996	474
Total liabilities	8,135	7,249
Shareholders' Equity		
Common shares, no par value, unlimited shares authorized 34,286,002 shares issued and outstanding as of December 31, 2022, 29,897,559 shares issued and outstanding as of December 31, 2021	273,900	251,901
Pre-funded warrants - 8,518,257 issued and outstanding as of December 31, 2022 and 12,327,780 as of December 31, 2021	34,352	52,941
Additional paid-in capital	24,437	15,711
Accumulated deficit	(266,341)	(207,953)
Total shareholders' equity	66,348	112,600
Total liabilities and shareholders' equity	$ 74,483	$ 119,849

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Loss
(in thousands of US dollars, except share and per share data)

	Years Ended December 31,	
	2022	**2021**
Revenue	$ 5,000	$ 15,000
Operating expenses		
Research and development, net of tax credits	$ 39,829	$ 38,671
General and administrative	15,718	12,399
Commercial	9,095	7,003
Loss from operations	(59,642)	(43,073)
Interest income, net	1,254	220
Net loss and comprehensive loss	$ (58,388)	$ (42,853)
Weighted average number of shares and pre-funded warrants outstanding, basic and diluted	42,450,316	41,833,861
Net loss per share, basic and diluted	$ (1.38)	$ (1.02)

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Shareholders' Equity
(in thousands of US dollars, except share data)

	Common Shares		Pre-funded warrants				
	Number of shares	Amount	Number of warrants	Amount	Additional paid-in capital	Accumulated deficit	Total
Balance as of December 31, 2020	29,827,997	$ 251,682	11,417,034	$ 48,007	$ 8,530	$ (165,100)	$ 143,119
Transactions during 2021							
Net loss	—	—	—	—	—	(42,853)	(42,853)
Exercise of stock options	69,562	219	—	—	(98)	—	121
Private Placement	—	—	910,746	4,934	—	—	4,934
Share-based compensation	—	—	—	—	7,279	—	7,279
Issuance of common shares, net of issuance costs	—	—	—	—	—	—	—
Balance as of December 31, 2021	29,897,559	$ 251,901	12,327,780	$ 52,941	$ 15,711	$ (207,953)	$ 112,600
Balance as of December 31, 2021	29,897,559	$ 251,901	12,327,780	$ 52,941	$ 15,711	$ (207,953)	**$** 112,600
Transactions during 2022							
Net loss	—	—	—	—	—	(58,388)	(58,388)
Exercise of stock options	217,684	742	—	—	(322)	—	420
Exercise of prefunded warrants, net of issuance costs	3,809,523	18,627	(3,809,523)	(18,589)	—	—	38
Share-based compensation	—	—	—	—	9,048	—	9,048
Issuance of common shares, net of issuance costs	361,236	2,630	—	—	—	—	2,630
Balance as of December 31, 2022	34,286,002	$ 273,900	8,518,257	$ 34,352	$ 24,437	$ (266,341)	$ 66,348

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Consolidated Statements of Cash Flows
(in thousands of US dollars)

	Year ended December 31,	
	2022	**2021**
Cash flows used in operating activities		
Net loss	$ (58,388)	$ (42,853)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation of property and equipment	89	93
Accretion/Amortization of investment discount/premium	(97)	—
Share-based compensation expense	9,048	7,279
Loss on disposals of property and equipment	141	—
Changes in operating assets and liabilities:		
Other receivables	(755)	96
Research and development tax credits receivable	25	369
Prepaid expenses	(1,706)	1,129
Operating lease assets and liabilities	81	26
Accounts payable and accrued liabilities	(907)	637
Net cash used in operating activities	(52,469)	(33,224)
Cash provided by (used in) investing activities		
Acquisition of property and equipment	(272)	—
Acquisition of short-term investments	(85,852)	(15,000)
Redemption of short-term investments	29,000	85,000
Net cash provided by (used in) investing activities	(57,124)	70,000
Cash provided by financing activities		
Proceeds from exercise of options	420	121
Proceeds from exercise of warrants	38	—
Issuance of common shares, net of issuance costs	2,630	—
Net Proceeds from issuance of pre-funded warrants in a private placement (note 6)	—	4,934
Cash provided by financing activities	3,088	5,055
Net increase (decrease) in cash and cash equivalents	(106,505)	41,831
Cash and cash equivalents – Beginning of year	114,141	72,310
Cash and cash equivalents – End of year	$ 7,636	$ 114,141

The accompanying notes are an integral part of these consolidated financial statements.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
(in thousands of US dollars, except share and per share data)

1 Organization and Nature of Operations

Milestone Pharmaceuticals Inc. (Milestone or the Company) is a biopharmaceutical company incorporated under the Business Corporations Act of Québec. Milestone is focused on the development and commercialization of innovative cardiovascular medicines. Milestone's lead product candidate, etripamil, is a novel, potent short-acting calcium channel blocker that the Company designed and is developing as a rapid-onset nasal spray to be -administered by patients. The Company is developing etripamil to treat paroxysmal supraventricular tachycardia, atrial fibrillation, and other cardiovascular indications.

2 Summary of Significant Accounting Policies

a) Basis of consolidation

The consolidated financial statements include the accounts of the Company and Milestone Pharmaceuticals USA, Inc. All intercompany transactions and balances have been eliminated.

b) Basis of Presentation and Use of Accounting Estimates

These consolidated financial statements of the Company have been presented in United States dollars (USD) and have been prepared in accordance with accounting principles generally accepted in the United States of America (U.S. GAAP), including the applicable rules and regulations of the Securities and Exchange Commission (SEC) regarding financial reporting.

The preparation of consolidated financial statements in conformity with US GAAP requires the Company to make estimates and judgments that affect certain reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the period. The Company bases its estimates and assumptions on current facts, historical experience and various other factors that it believes are reasonable under the circumstances, to determine the carrying values of assets and liabilities that are not readily apparent from other sources. Significant estimates and judgments include, but are not limited to,

- Estimates of the percentage of work completed of the total work over the life of the individual trial in accordance with agreements established with CROs, CMOs and clinical trial sites which in turn impact the research & development expenses.

- Estimate of the grant date fair value share options granted to employees, consultants and direct, and the resulting share-based compensation expense, using the Black-Scholes option-pricing model.

Estimates and assumptions about future events and their effects cannot be determined with certainty and therefore require the exercise of judgment. As of the date of issuance of these consolidated financial statements, the Company is not aware of any specific event or circumstance that would require the Company to update its estimates, assumptions and judgments. These estimates may change as new events occur and additional information is obtained and are recognized in the consolidated financial statements as soon as they become known. Actual results could differ from those estimates and any such differences may be material to the Company's consolidated financial statements.

c) Segment Information

The Company manages its operations as a single operating segment for the purposes of assessing performance and making operating decisions while focusing on the development and commercialization of innovative cardiovascular medicines.

d) Revenue Recognition

Collaborative Arrangements

The Company considers the nature and contractual terms of arrangements and assesses whether an arrangement involves a joint operating activity pursuant to which the Company is an active participant and is exposed to significant risks and rewards dependent on the commercial success of the activity. If the Company is an active participant and is exposed to significant risks and rewards dependent on the commercial success of the activity, the Company accounts for such an arrangement as a collaborative arrangement under Accounting Standards Codification (ASC) 808, Collaborative Arrangements (ASC 808), which requires that certain transactions between the Company and collaborators be recorded in its consolidated statements of comprehensive loss on either a gross basis or net basis, depending on the characteristics of the collaborative relationship, and requires enhanced disclosure of collaborative relationships. The Company evaluates its collaboration agreements for proper classification in its consolidated statements of comprehensive loss based on the nature of the underlying activity. If payments to and from collaborative partners are not within the scope of other authoritative accounting literature, the consolidated statements of loss classification for the payments is based on a reasonable, rational analogy to authoritative accounting literature that is applied in a consistent manner. If the Company concludes that it has a customer relationship with one of its collaborators, the Company follows the guidance in Accounting Standards Codification (ASC) Topic 606, Revenue From Contracts With Customers (ASC 606).

Revenue from Contracts with Customers

In accordance with ASC 606, revenue is recognized when a customer obtains control of promised goods or services. The amount of revenue recognized reflects the consideration to which the Company expects to be entitled in exchange for these goods and services. To achieve this core principle, the Company applies the following five steps: 1) identify the customer contract; 2) identify the contract's performance obligations; 3) determine the transaction price; 4) allocate the transaction price to the performance obligations; and 5) recognize revenue when or as a performance obligation is satisfied. The Company evaluates all promised goods and services within a customer contract and determines which of such goods and services are separate performance obligations. This evaluation includes an assessment of whether the good or service is capable of being distinct and whether the good or service is separable from other promises in the contract. In assessing whether promised goods or services in licensing arrangements are distinct, the Company considers factors such as the stage of development of the underlying intellectual property and the capabilities of the customer to develop the intellectual property on their own or whether the required expertise is readily available. Licensing arrangements are analyzed to determine whether the promised goods or services, which often include licenses, research and development services and governance committee services, are distinct or whether they must be accounted for as part of a combined performance obligation. If the license is considered not to be distinct, the license would then be combined with other promised goods or services as a combined performance obligation. If the Company is involved in a governance committee, it assesses whether its involvement constitutes a separate performance obligation. When governance committee services are determined to be separate performance obligations, the Company determines the fair value to be allocated to this promised service. Certain contracts contain optional and additional items, which are considered marketing offers and are accounted for as separate contracts with the customer if such option is elected by the customer, unless the option provides a material right which would not be provided without entering into the contract. An option that is considered a material right is accounted for as a separate performance obligation. The transaction price is determined based on the consideration to which the Company will be entitled in exchange for transferring goods and services to the customer. A contract may contain variable consideration, including potential payments for both milestone and research and development services. For certain potential milestone payments, the Company estimates the amount of variable consideration by using the most likely amount method. In making this assessment, the Company evaluates factors such as the clinical, regulatory, commercial and other risks that must be overcome to achieve the milestone. Each reporting period the Company re-evaluates the probability of achievement of such variable consideration and any related constraints. Milestone will include variable consideration, without constraint, in the transaction price to the extent it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

If the contract contains a single performance obligation, the entire transaction price is allocated to the single performance obligation. Contracts that contain multiple performance obligations require an allocation of the transaction price among the performance obligations on a relative standalone selling price basis unless a portion of the transaction price is variable and meets the criteria to be allocated entirely to a performance obligation or to a distinct good or service that forms part of a single performance obligation.

The Company allocates the transaction price based on the estimated standalone selling price of the underlying performance obligations or in the case of certain variable consideration to one or more performance obligations. The Company must develop assumptions that require judgment to determine the stand-alone selling price for each performance obligation identified in the contract. The Company utilizes key assumptions to determine the stand-alone selling price, which may include other comparable transactions, pricing considered in negotiating the transaction and the estimated costs to complete the respective performance obligation. Certain variable consideration is allocated specifically to one or more performance obligations in a contract when the terms of the variable consideration relate to the satisfaction of the performance obligation and the resulting amounts allocated to each performance obligation are consistent with the amount the Company would expect to receive for each performance obligation.

When a performance obligation is satisfied, revenue is recognized for the amount of the transaction price, excluding estimates of variable consideration that are constrained, that is allocated to that performance obligation on a relative standalone selling price basis. Significant management judgment is required in determining the level of effort required under an arrangement and the period over which the Company is expected to complete its performance obligations under an arrangement.

For performance obligations consisting of licenses and other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from non- refundable, up-front fees. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition. If the license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company will recognize revenue from non-refundable, up-front fees allocated to the license at the point in time when the license is transferred to the customer and the customer is able to use and benefit from the license.

e) Cash and Cash Equivalents

Cash and cash equivalents consist of cash and highly liquid investments that are readily convertible into cash with original maturities of three months or less at acquisition date.

f) Short-Term Investments

Short-term investments are classified as held-to-maturity, are initially recognized at fair value and are subsequently accounted for at amortized cost. They are comprised of guaranteed investment certificates with a maturity greater than 90 days but less than one year and, as such, are classified as current assets.

g) Concentration of Credit Risk

Financial instruments that potentially subject the Company to concentration of credit risk consist primarily of cash and cash equivalents and investment securities classified as held to maturity. The Company maintains deposits in financial institutions. Management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. Additionally, the Company has adopted an investment policy that includes guidelines relative to credit quality, diversification of maturities and liquidity.

h) Currency Risk

The Company is exposed to currency risk due to financial instruments denominated in foreign currencies. The Company is exposed to the Canadian dollar currency risk and does not enter into arrangements to hedge its currency risk exposure.

i) Property and Equipment

Property and equipment is stated at historical cost less accumulated amortization. Expenditures for maintenance and repairs are recorded to expense as incurred. The Company reviews its property and equipment whenever events or changes in circumstances indicate that the carrying value of certain assets might not be recoverable and recognizes an impairment loss when it is probable that an asset's realizable value is less than the carrying value. To date, no such impairment losses have been recorded. Amortization is calculated using the straight-line method over the following estimated useful lives of the assets:

Computer hardware and software	3 years
Office equipment	5 years
Furniture and fixtures	5 years
Leasehold improvements	over the lease-term

j) Leases

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company does not have financing leases.

Operating lease liabilities and their corresponding right-of-use assets are initially recorded based on the present value of lease payments over the expected remaining lease term. Right-out-use assets are subsequently accounted for as long-lived assets, including evaluating for indicators of impairment. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate to discount lease payments, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. Prospectively, the Company will adjust the right-of-use assets for straight-line rent expense or any incentives received and remeasure the lease liability at the net present value using the same incremental borrowing rate that was in effect as of the lease commencement or transition date.

The Company has elected not to recognize leases with an original term of one year or less on the balance sheet. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company's assessment unless there is reasonable certainty that the Company will renew.

k) Pre-funded Warrants

Pre-funded warrants allow the holder to pay little or no consideration to receive the shares upon exercise of the warrant. The pre-funded warrants do not meet the definition of a derivative under ASC 815 because their fair value at issuance is equal to the fair value of the shares underlying the warrant. As such, they have the characteristics of a prepaid forward sale of equity. As a result, the pre-funded warrants are accounted for as equity instruments.

l) Share Issuance Costs

Share issuance costs applicable to the issuance of equity instruments are recorded as a reduction of the financing equity proceeds.

m) Research and Development and Investment Tax Credits

Research and development costs are charged to expense as costs are incurred in performing research and development activities. The Company's research and development costs consist primarily of salaries and fees paid to contract research organizations (CROs) and to contract manufacturing organizations (CMOs).

Clinical trial expenses include direct costs associated with CROs, direct CMO costs for the formulation and packaging of clinical trial material, as well as investigator and patient related costs at sites at which the Company's trials are being conducted. Direct costs associated with the Company's CROs and CMOs are generally payable on a time and materials basis, or when milestones are achieved. The invoicing from clinical trial sites can lag several months. The Company records expenses for its clinical trial activities performed by third parties based upon estimates of the percentage of work completed of the total work over the life of the individual study in accordance with agreements established with CROs and clinical trial sites. The Company determines the estimates through discussions with internal clinical personnel, CROs and CMOs as to the progress or stage of completion of trials or services and the agreed upon fee to be paid for such services based on facts and circumstances known to the Company as of each consolidated balance sheet date. The actual costs and timing of clinical trials are highly uncertain, subject of risks and may change depending upon a number of factors, including the Company's clinical development plan. If the actual timing of the performance of services of the level of effort varies from the estimate, the Company will adjust the accrual accordingly.

The Company recognizes the benefit of Canadian research and development tax credits as a reduction of research and development costs for fully refundable investment tax credits and as a reduction of income taxes for investment tax credits that can only be claimed against income taxes payable when there is reasonable assurance that the claim will be recovered.

n) Income Taxes

The provision for income taxes is computed using the liability method. Under this method, deferred tax assets and liabilities are determined based on differences between financial reporting and tax bases of assets and liabilities. Deferred tax assets and liabilities are measured using enacted tax rates and laws that will be in effect when the differences are expected to reverse. A valuation allowance is recorded to reduce the carrying amount of deferred income tax assets until when it is more likely than not that these assets will be realized. Tax benefits related to tax positions not deemed to meet the "more-likely-than-not" threshold are not permitted to be recognized in the consolidated financial statements.

o) Foreign Currency Translation and Transactions

The functional currency of the Company is the US dollar. Accordingly, transactions denominated in currencies other than the functional currency are measured and recorded in the functional currency at the exchange rate in effect on the date of the transactions. At each consolidated balance sheet date, monetary assets and liabilities denominated in currencies other than the functional currency are remeasured using the exchange rate in effect at that date. Non-monetary assets and liabilities and revenue and expense items denominated in foreign currencies are translated into the functional currency using the exchange rate prevailing at the dates of the respective transactions. Any gains or losses arising on remeasurement are included in the consolidated statement of operations.

p) Share Based Compensation

The Company has a share based compensation plan which is described in detail in note 8 and records all share-based payments, including grants of employee share options, at their fair values. The fair value of share options granted to employees and non-employees is estimated at the date of grant using the Black-Scholes option pricing model. The Company recognizes share based compensation expense over the requisite service period of the individual grants, which equals the vesting period, using the straight-line method. Forfeitures, if any, are recorded as they occur. Any consideration paid by employees on exercising share options and the corresponding portion previously credited to contributed surplus are credited to share capital. The Black-Scholes option pricing model used by the Company to calculate option values was developed to estimate fair value.

The Company approved an employee share purchase plan in April 2019, which became effective on May 8, 2019 and is described in note 8. The plan provides a means by which eligible employees of the Company and certain designated companies may be given an opportunity to purchase common shares. The plan permits the Company to grant a series of purchase rights to eligible employees under an employee stock purchase plan.

q) Recently Adopted Accounting Pronouncements

The Company has considered recent accounting pronouncements and concluded that they are either not applicable to the business or that the effect is not expected to be material to the consolidated financial statements as a result of future adoption.

r) Significant Risks and Uncertainties

The Company is subject to challenges and risks specific to its business and its ability to execute on its strategy, as well as risks and uncertainties common to companies in the pharmaceutical industry, including, without limitation, risks and uncertainties associated with: obtaining regulatory approval of its product candidate; delays or problems in the supply of its study drug or failure to comply with manufacturing regulations; identifying, acquiring or in-licensing product candidates; pharmaceutical product development and the inherent uncertainty of clinical success; and the challenges of protecting and enhancing its intellectual property rights; and complying with applicable regulatory requirements.

Further, the Company may be impacted by general economic, political, and market conditions, including deteriorating market conditions due to investor concerns regarding inflation and Russian hostilities in Ukraine and overall fluctuations in the financial markets in the U.S. and abroad.

s) Sources of Liquidity and Funding Requirements

The Company has incurred operating losses and experienced negative operating cash flows since its inception and anticipates to continue to incur losses for at least the next several years. As of December 31, 2022, the Company had cash and cash equivalents and short-term investments of $64.5 million and an accumulated deficit of $266.3 million.

The Company believes that its cash and cash equivalents as of December 31, 2022, in addition to the financing agreement (see Note 16) signed on March 27, 2023, which provides $50 million of cash, are sufficient for the Company to fund planned operations for at least one year from the issuance date of these consolidated financial statements. The Company has historically financed its operations primarily through the sale of equity securities and, to a lesser extent from cash received pursuant to its license agreement. To date, the Company has not generated any revenue from product sales. Management expects operating losses and negative cash flows from operations to continue for the foreseeable future. The Company currently plans to raise additional funding as required based on the status of its clinical trials and projected cash flows. There can be no assurance that, in the event the Company requires additional financing, such financing will be available at terms acceptable to the Company, if at all. Failure to generate sufficient cash flows from operations, raise additional capital and reduce discretionary spending should additional capital not become available could have a material adverse effect on the Company's ability to achieve its business objectives.

3 Revenue

General

To date, the Company generated revenue of $5.0 million and $15.0 million for the year ended December 31, 2022 and December 31, 2021, respectively. This revenue is from the license agreement with Ji Xing and is comprised of upfront and milestone payments.

Strategic Partnerships

Ji Xing

On May 15, 2021, the Company entered into the License Agreement with Ji Xing, which is an entity affiliated with RTW Investments, LP, or RTW, a beneficial owner of approximately 13% of the Company's common shares, as of December 31, 2022. Under the License Agreement, the Company granted Ji Xing exclusive development and commercialization rights to any pharmaceutical product that uses a device to deliver the Company's proprietary calcium channel blocker known as etripamil by nasal spray for all prophylactic and therapeutic uses in humans in the following territories: People's Republic of China, including mainland China, Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan (the Territory). Ji Xing will be responsible for development and regulatory activities in the Territory, and the Company will remain responsible for certain manufacturing activities in the Territory, subject to the supply agreement subsequently entered into by the Company and Ji Xing as contemplated by the License Agreement (the Supply Agreement). The Company received a non-refundable upfront cash payment of $15 million and the right to future payments of up to $107.5 million in total development and sales milestone payments. In addition, the Company is entitled to receive tiered royalty payments ranging from a percentage in the low double digits to the high double digits of Net Sales (as defined in the License Agreement) of all products sold in the Territory. The Company received $5 million in milestone payments during the year ended December 31, 2022. These milestone payments were reached as a result of the successful completion of our Phase 3 clinical trial in the U.S. for the treatment of PSVT and the initiation of a Phase 3 clinical trial for etripamil in mainland China.

Management evaluated all of the promised goods or services within the contract and determined that such goods and services were separate performance obligations. The Company determined that the license granted was a separate performance obligation as Ji Xing can benefit from the license granted on its own after the transfer of the license, as it does not require any significant development, regulatory or commercialization activities from Milestone. Ji Xing is responsible for all development, regulatory and commercialization activities in the Territory, including the performance of clinical trials necessary for regulatory approval, and is responsible for all such related costs. Supply of the product can be provided by another entity, as the Company currently uses a CMO for the production of etripamil without subsequent significant modification or customization by the Company, therefore the Company determined the obligation to supply product is a separate and distinct obligation. The Company concluded that the obligation for participation on the various governance committees was distinct as the services could be performed by an outside party, however it was determined to be immaterial after estimating the stand-alone cost compared to the License Agreement as a whole. As a result, the Company concluded there were two material and distinct performance obligations to account for under ASC 606 at the inception of the License Agreement.

The Company determined that the transaction price consists of the $15 million non-refundable upfront cash payment and the constrained variable consideration of the development milestone payments. As the development milestones are contingent on occurrences out of the direct control of the Company, the estimate of the variable consideration is $0. Variable constraint does not apply to sales- or usage-based royalties derived from the licensing of Intellectual property; rather, consideration from such royalties is only recognized as revenue at the later of when the performance obligation is satisfied or when the uncertainty is resolved (e.g., when subsequent sales or usage occurs), therefore the sales and royalty milestones are not included in the transaction price. The Company will re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved, or other changes in circumstances occur, adjust its estimate of the transaction price if necessary. For the year ended December 31, 2022, the Company has recognized the $5 million of the $107.5 million in future milestone payments as revenue, for the reasons described in the preceding paragraph.

Concurrent with the License Agreement, Ji Xing acquired $5 million of pre-funded warrants (see note 8). The Company considered whether this equity investment should be evaluated as part of the transaction price and concluded that as the fair value of the company's common shares on a per share basis was equal to the fair value of the pre-funded warrants at the date of the investment, there was no premium or discount on the shares that should be allocated and included in the transaction price. The Company accounted for the issuance of pre-funded warrants as equity and included in basic and diluted loss per share in the accompanying financial statements. See note 8 for additional details.

For any future subsequent purchases of product pursuant to the Supply Agreement, each order will be accounted for as a separate purchase and the order price will be allocated to the products based on the standalone selling price of the products. Under this methodology, the order price will be allocated to the single performance obligation to supply the products. As the Company has not previously licensed a product for a territory, the residual approach was used by deducting the estimated stand-alone selling price of the other obligations from the total transaction price to determine the stand-alone selling price of the remaining goods and services, which consisted of the transfer of intellectual property pursuant to the license. Therefore, the remaining transaction price of $15 million was allocated to the technology transfer and recognized at a point in time when the technology has been transferred. The technology transfer was completed on June 22, 2021, and the $15 million was recognized at that point in time as revenue in the related statement of comprehensive loss.

4 Short-term Investments

For the year ended December 31, 2022, the short-term investments of $56.9 million were comprised of term deposits issued in US currency, earning interest between 3.14% and 5.18%, maturing between January 3, 2023 and May 2, 2023. These short-term investments were in scope of ASC 320, Investments-Debt Securities. The short-term investments maturity is greater than 90 days but less than one year, and they were classified as held to maturity, recorded as current assets and were accounted for at amortized cost. Interest income earned on short-term investments is reported in interest income, net. The Company had no short-term investments for the year ended December 31, 2021.

5 Leases

On May 20, 2022, the Company entered into a new lease arrangement for a 62-month term for new office space located in Charlotte, NC. The Company recognized the operating lease right-of-use asset and operating lease liabilities at the lease commencement date on August 1, 2022. The interest rate implicit in lease contracts is not readily determinable and the Company does not have a public credit rating and carries no debt. As such, several factors were considered in the determination of the Company's incremental borrowing rate used in determining the present value of lease payments. The Company's examined credit ratings for similar companies, assumed equivalency between the Canadian and U.S. markets for collateralized debt and used rates near the 62-month period. This resulted in an incremental borrowing rate of 7.55%. Lease expenses are recognized on a straight-line basis over the lease term, which is accomplished by increasing the amortization of the right-of-use asset as interest expense on the lease liability declines over the lease term.

On July 1, 2020, the Company entered into an arrangement for the lease renewal for its headquarters located in Ville Saint-Laurent, Quebec. The 5-year lease term is from December 1, 2020 expiring on November 30, 2025. The Company revalued the operating lease right-of-use asset and operating lease liabilities at the effective lease arrangement date of July 1, 2020. The Company's examined credit ratings for similar companies, assumed equivalency between the Canadian and U.S. markets for collateralized debt and used rates for the remaining lease term of 65 months. This resulted in an incremental borrowing rate of 5.26%. Lease expenses are recognized on a straight-line basis over the lease term, which is accomplished by increasing the amortization of the right-of-use asset as interest expense on the lease liability declines over the lease term. The Company is not reasonably certain of renewing the lease following the current renewal option and recognized the right-of-use asset and operating lease liabilities to November 30, 2025.

On June 3, 2019, the Company entered into a lease arrangement for a three-year term for its office located in Charlotte, NC. The Company recognized the operating lease right-of-use asset and operating lease liabilities at the lease commencement date on September 10, 2019. The interest rate implicit in lease contracts is not readily determinable and the Company does not have a public credit rating and carries no debt. As such, several factors were considered in the determination of the Company's incremental borrowing rate used in determining the present value of lease payments. The Company's examined credit ratings for similar companies, assumed equivalency between the Canadian and U.S. markets for collateralized debt and used rates over the three-year period. This resulted in an incremental borrowing rate of 8%. Lease expenses are recognized on a straight-line basis over the lease term, which is accomplished by increasing the amortization of the right-of-use asset as interest expense on the lease liability declines over the lease term. The company

(in thousands of US dollars, except share and per share data)

recognized the right-of-use asset and operating lease liabilities over the three-year period ending September 30, 2022. This lease was terminated as of September 30, 2022.

The Company's two operating office leases right-of-use assets as at December 31 were as follows:

	2022	2021
Opening balance	$ 711	$ 980
New operating lease right-of-use asset	2,103	—
Amortization of right-of-use asset	(391)	(269)
Closing balance	$ 2,423	$ 711

Operating lease expenses of $490 and $314 are included in general and administrative operating expenses in the consolidated statement loss and comprehensive loss, and within operating activities in the statement of cash flows for the year ended December 31, 2022 and 2021, respectively and are comprised of two operating lease right-of-use assets and one operating lease of less than 12 months.

The following table summarizes the future minimum lease payments of right-of-use assets operating lease as at December 31, 2022:

January 1, 2023 to December 31, 2023	657
January 1, 2024 to December 31, 2024	669
January 1, 2025 to December 31, 2025	667
January 1, 2026 to December 31, 2026	530
January 1, 2027 to September 30, 2027	406
	2,929
Less interest	(438)
	$ 2,491

6 Property and equipment

Property and equipment consist of the following at December 31:

	2022	2021
Computer hardware and software	$ 120	$ 22
Office equipment	155	406
Leasehold improvements	102	26
Total	$ 377	$ 454
Less accumulated depreciation	(120)	(239)
Property and equipment, net	$ 257	$ 215

During the year ended December 31, 2022, the Company recorded a disposal of $348, which resulted in a loss of $141. No disposal was recorded for the year ended December 31, 2021. For the year ended December 31, 2022 and 2021, depreciation expense was $89 and $93, respectively and was included in research and development expense.

(in thousands of US dollars, except share and per share data)

7 Accounts payable and accrued liabilities

Accounts payable and accrued liabilities comprised the following as of December 31:

	December 31, 2022	December 31, 2021
Trade accounts payable	$ 2,263	$ 4,384
Accrued compensation and benefits payable	2,573	1,458
Accrued research and development liabilities	404	272
Other accrued liabilities	404	437
Total	$ 5,644	$ 6,551

8 Shareholders' Equity

Authorized Share Capital

The Company has authorized and issued common shares, voting and participating, without par value, of which unlimited shares were authorized and 34,286,002 shares were issued and outstanding as of December 31, 2022.

As of December 31, 2022, there were 1,121,076 common shares available for issuance under the Employee Stock Purchase Plans and no common shares have been issued under such plan.
In August 2022, the Company issued and sold 361,236 common shares under the Open Market Sale AgreementSM, or the Sales Agreement, with Jefferies LLC with respect to an at-the-market offering program, or the ATM Program, for proceeds of $2.6 million (net of issuance costs of $0.1 million).

Shelf Registration

On November 12, 2021, the company entered into an agreement and the company may sell any combination of the securities described in this prospectus in one or more offerings up to a total aggregate offering price of $250,000,000.

Pre-funded Warrants – Private Placement

On May 15, 2021, the Company entered into a securities purchase agreement to sell and issue in a private placement pre-funded warrants to purchase up to 910,746 of the Company's common shares, at a purchase price of $5.48 per pre-funded warrant pursuant to the License Agreement for aggregate net proceeds of $5.0 million (the Private Placement). The Private Placement closed on May 21, 2021. Each pre-funded warrant is exercisable for one of the Company's common shares at an exercise price of $0.01 per share, has no expiration date, and is immediately exercisable, subject to certain beneficial ownership limitations. The pre-funded warrants are classified and accounted for as equity.

Open Market Sale Agreement

On July 29, 2020, the Company entered into an Open Market Sale Agreement℠ with respect to an at-the-market offering program (ATM Program) under which the Company may issue and sell its common shares having an aggregate offering price of up to $50 million. The Company has not sold shares under the ATM program as of the date of this filing.

Pre-funded Warrants and Common Shares – Public Offering

On October 22, 2020, the Company issued (i) 5,095,897 common shares, without par value, at a price to the public of $5.25 per share, and (ii) pre-funded warrants to purchase 4,761,903 common shares at an exercise price equal to $0.01 per share, at a price to the public of $5.24 per common share underlying the pre-funded warrants (the Offering). The net proceeds to the Company from the Offering were $48.2 million. In October 2022, 3,809,523 common shares of the pre-funded warrants were exercised at $0.01 per share. The remaining pre-funded warrants are classified and accounted for as equity.

(in thousands of US dollars, except share and per share data)

Additional Paid-in Capital

	2022	2021
Opening balance	$ 15,711	$ 8,530
Share-based compensation expense	9,048	7,279
Exercise of stock options	(322)	(98)
Closing balance	$ 24,437	$ 15,711

9 Share Based Compensation

Under the Company's 2019 Equity Incentive Plan (the 2019 Plan) and the Company's Stock Option Plan (the 2011 Plan), unless otherwise decided by the Board of Directors, options vest and are exercisable as follows: 25% vest and are exercisable on the one year anniversary of the grant date and one thirty-sixth ($1/36^{th}$) of the remaining options vest and are exercisable each month thereafter, such that options are vested in full on four-year anniversary of the grant date.

On November 10, 2021, the Company established an 2021 Inducement Plan under Nasdaq Marketplace Rules through the granting of awards. This 2021 Inducement Plan is intended to help the Company provide an inducement material for certain individuals to enter into employment with the Company, incentives for such persons to exert maximum efforts for the success of the Company and provide a means by which employees may benefit from increases in value of the common shares. There were 523,000 granted and 20,000 options cancelled for the year ended December 31, 2022. As of December 31, 2022, there were 1,000,000 shares available for issuance under the 2021 Inducement Plan, of which 497,000 shares were available for future grants.

On January 1, 2022 and on July 5, 2022, the number of the Company's common shares reserved for issuance under the 2019 Plan increased by 1,195,902 and 1,000,000 common shares, respectively. In addition, 125,323 options have been forfeited under the 2011 Plan after adoption of the 2019 Plan and became available for issuance under the 2019 Plan. As of December 31, 2022, there were 6,811,506 shares available for issuance under the 2019 Plan, of which 1,433,105 shares were available for future grants.

On July 15, 2022, the Company offered an Employee Share Purchase Plan, or ESPP, in which participation is available to substantially all of our employees in the United States and Canada who meet certain service eligibility requirements. As of December 31, 2022, the Company has 1,121,076 common shares available under the ESPP with no common shares issued under this plan.

Milestone Pharmaceuticals Inc.
Notes to Consolidated Financial Statements
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The total outstanding and exercisable options from the 2011 Plan, 2019 Plan and Inducement Plan as of December 31 were as follows:

	2022				
	Number of shares				Weighted average exercise price
	2019 Plan	Inducement Plan	2011 Plan	Total	
Outstanding at beginning of year - 2011 Plan	$ —	—	$ 1,995,971	1,995,971	$ 2.07
Outstanding at beginning of year - 2019 Plan	3,749,834	—	—	3,749,834	9.52
Granted - 2019 Plan	1,790,700	—	—	1,790,700	5.76
Granted - Inducement Plan	—	523,000	—	523,000	6.37
Exercised - 2019 Plan	(45,089)	—	—	(45,089)	3.83
Exercised - 2011 Plan	—	—	(172,595)	(172,595)	1.43
Forfeited - Inducement Plan	—	(20,000)	—	(20,000)	5.48
Forfeited - 2019 Plan	(181,133)	—	—	(181,133)	8.00
Forfeited - 2011 Plan	—	—	(19,583)	(19,583)	9.35
Expired - 2011 Plan	—	—	(1,121)	(1,121)	0.96
Outstanding at end of period	$ 5,314,312	503,000	1,802,672	7,619,984	$ 6.73
Outstanding at end of period - Weighted average exercise price	$ 8.35	6.41	$ 2.05		
Exercisable at end of period	2,390,549	—	1,800,546	4,191,095	$ 6.52
Exercisable at end of period - Weighted average exercise price	$ 9.90	—	$ 2.04		

	2021				
	Number of shares				Weighted average exercise price
	2019 Plan	Inducement Plan	2011 Plan	Total	
Outstanding at beginning of year - 2011 Plan	$ —	—	$ 2,080,087	2,080,087	$ 2.15
Outstanding at beginning of year - 2019 Plan	1,706,190	—	—	1,706,190	13.55
Granted - 2019 Plan	2,137,250	—	—	2,137,250	6.22
Exercised - 2019 Plan	(19,000)	—	—	(19,000)	3.74
Exercised - 2011 Plan	—	—	(50,562)	(50,562)	0.98
Forfeited - 2019 Plan	(74,606)	—	—	(74,606)	8.73
Forfeited - 2011 Plan	—	—	(31,841)	(31,841)	9.42
Expired - 2011 Plan	—	—	(1,713)	(1,713)	0.95
Outstanding at end of period	3,749,834	—	1,995,971	5,745,805	$ 6.93
Outstanding at end of period - Weighted average exercise price	$ 9.52	—	$ 2.07		
Exercisable at end of period	1,094,316	—	1,795,332	2,889,648	$ 5.60
Exercisable at end of period - Weighted average exercise price	$ 11.48	—	$ 2.01		

The weighted average remaining contractual life was 7.47 and 7.81 years for outstanding options as of December 31, 2022 and 2021, respectively. The weighted average remaining contractual life was 6.37 and 6.80 years for vested options, as of December 31, 2022 and 2021, respectively.

There was $15.7 million and $15.3 million total unrecognized compensation cost related to non-vested share options as of December 31, 2022 and 2021, respectively. The share options are expected to be recognized over a remaining weighted average vesting period of 2.36 years and 2.42 years as of December 31, 2022 and 2021, respectively.

(in thousands of US dollars, except share and per share data)

The non-vested options as of December 31 were as follows:

	2022				
	Number of options				Weighted average fair value
	2019 Plan	Inducement Plan	2011 Plan	Total	
Non-vested share options at beginning of year - 2011 Plan	—	—	200,639	200,639	$ 1.86
Non-vested share options at beginning of year - 2019 Plan	2,655,518	—	—	2,655,518	6.40
Granted - 2019 Plan	1,790,700	—	—	1,790,700	4.37
Granted - Inducement Plan	—	523,000	—	523,000	4.81
Vested, outstanding 2011 Plan	—	—	(198,317)	(198,317)	1.81
Vested, outstanding 2019 Plan	(1,376,791)	—	—	(1,376,791)	6.19
Forfeited - 2011 Plan	—	—	(196)	(196)	1.91
Expired - 2019	—	—	—	—	5.03
Forfeited - Inducement Plan		(20,000)		(20,000)	4.18
Forfeited - 2019 Plan	(145,664)	—	—	(145,664)	5.49
Non-vested share options at end of period	2,923,763	503,000	2,126	3,428,889	$ 5.24
Non-vested share options at end of period - Weighted average fair value	$ 5.31	$ 5.31	$ 6.64		

	2021				
	Number of options				Weighted average fair value
	2019 Plan	Inducement Plan	2011 Plan	Total	
Non-vested share options at beginning of year - 2011 Plan	—	—	543,192	543,192	$ 1.81
Non-vested share options at beginning of year - 2019 Plan	1,438,026	—	—	1,438,026	10.28
Granted - 2019 Plan	2,137,250	—	—	2,137,250	4.70
Vested, outstanding 2011 Plan	—	—	(333,741)	(333,741)	1.65
Forfeited - 2011 Plan	—	—	(8,812)	(8,812)	6.66
Forfeited - 2019 Plan	(63,303)	—	—	(63,303)	6.28
Vested, outstanding 2019 Plan	(856,455)	—	—	(856,455)	8.69
Non-vested share options at end of period	2,655,518	—	200,639	2,856,157	$ 6.08
Non-vested share options at end of period - Weighted average fair value	$ 6.40	$ —	$ 1.86		

Options granted are valued using the Black-Scholes option pricing model. Amortization of the fair value of the options over vesting years has been expensed and credited to additional paid-in capital in shareholders' equity.

The following table summarizes information with respect to share options outstanding as of December 31, 2022:

	Options outstanding			Options exercisable		
Exercise price	Number of options	Weighted average remaining contractual life (years)	Weighted average exercise price	Number of options	Weighted average remaining contractual life (years)	Weighted average exercise price
$0.84-$1.73	1,043,673	4.15	$ 1.42	1,043,673	4.15	$ 1.42
$1.74-$3.20	723,094	5.81	$ 2.59	723,094	5.81	$ 2.59
$3.21-$5.25	644,250	7.47	$ 3.79	612,250	7.35	$ 3.74
$5.26-$6.36	3,554,925	8.62	$ 5.89	1,042,718	8.09	$ 6.11
$6.37-$8.50	689,300	9.16	$ 6.86	43,334	7.75	$ 7.10
$8.51-$15.50	57,905	7.50	$ 9.08	33,779	6.15	$ 9.42
$15.51-$20.50	76,620	6.50	$ 17.27	69,574	6.46	$ 17.32
$20.51-$22.45	830,217	6.84	$ 21.65	622,673	6.79	$ 21.67
Total	7,619,984	7.47	$ 6.73	4,191,095	6.37	$ 6.52

(in thousands of US dollars, except share and per share data)

The intrinsic value of all outstanding options as of December 31, 2022 was $3.8 million, based on the fair value of our common shares of $3.96 per share at December 31, 2022.

The fair value of share-based payment transaction is measured using Black-Scholes valuation model. This model also requires assumptions, including expected option life, volatility, risk-free interest rate and dividend yield, which greatly affect the calculated values:

	2022	2021
Exercise price	$ 5.90	$ 6.22
Share price	$ 5.90	$ 6.22
Volatility	92 %	93 %
Risk-free interest rate	2.43 %	1.05 %
Expected life	6.03 years	6.01 years
Dividend	0 %	0 %

Expected volatility is determined using comparable companies for which the information is publicly available. The risk-free interest rate is determined based on the U.S. sovereign rates benchmark in effect at the time of grant with a remaining term equal to the expected life of the option. Expected option life is determined based on the simplified method as the Company does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate expected term. The simplified method is an average of the contractual term of the options and its ordinary vesting period. Dividend yield is based on the share option's exercise price and expected annual dividend rate at the time of grant.

The Company recognized share-based compensation expense as follows for the year ended December 31:

	2022	2021
Administration	$ 4,229	$ 3,011
Research and development	3,483	3,046
Commercial activities	1,336	1,222
Total	$ 9,048	$ 7,279

10 Net loss per share

Basic and diluted net loss per common share is determined by dividing net loss applicable to common shareholders by the weighted average number of common shares and pre-funded warrants outstanding during the period. Share-based compensation shares have been excluded from the calculation because their effects would be anti-dilutive. Therefore, the weighted average number of shares used to calculate both basic and diluted loss per share are the same.

The following potentially dilutive securities have been excluded from the computation of diluted weighted average shares outstanding as of December 31, 2022 and 2021, as they would be anti-dilutive:

	2022	2021
Share options	7,619,984	5,745,805

Amounts in the table above reflect the common share equivalents of the noted instruments.

(in thousands of US dollars, except share and per share data)

11 Income taxes

A reconciliation between tax expense and the product of accounting income multiplied by the basic income tax rate for the years ended December 31, 2022 and 2021 is as follows:

	2022	2021
Loss before income taxes	$ (58,388)	$ (42,853)
Basic income tax rate	26.50 %	26.19 %
Computed income tax recovery	(15,473)	(11,221)
Effect on income tax rate resulting from		
Accounting charges not deductible for tax purposes	13	18
Non-deductible share-based compensation	2,704	1,929
Share issue costs	32	15
Accretion of investments	(26)	—
Tax benefits of current period losses and other tax assets	12,387	9,536
Valuation allowance for prior year adjustment	112	(276)
Other	251	(1)
Income tax expense recovery reported in the consolidated statements of loss and comprehensive loss	$ —	$ —

The Company has incurred Canadian federal and provincial net operating losses (NOLs) from inception. As of December 31, 2022, the Company has NOL carry-forwards of approximately $184.3 million and $181.4 million, respectively, for Canadian federal and Québec purposes, available to reduce future taxable income, which expire beginning in 2026 through 2042. The Company also has scientific research and experimental development expenditures of approximately $21.9 million and $26.5 million, respectively, for Canadian federal and Québec income tax purposes, which have not been deducted. These expenditures are available to reduce future taxable income and have an unlimited carry-forward period. Research and development tax credits and expenditures are subject to verification by the tax authorities, and, accordingly, these amounts may vary.

The Company has incurred NOLs for U.S. tax purposes. As of December 31, 2022, the Company has carry-forwards of approximately $38.1 million related to U.S. NOLs that may be carried forward indefinitely and are available to reduce future taxable income.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The net deferred tax assets have not been recognized in these financial statements because the criteria for recognition of these assets were not met.

The Company's deferred tax assets consist of the following for the years ended December 31, 2022 and 2021:

	2022	2021
Net operating loss carry-forwards	$ 57,952	$ 45,756
Tax basis of property and equipment in excess of carrying values	97	103
Federal SR&ED investment tax credits	545	709
Taxation of federal SR&ED investment tax credits	(82)	(108)
Research and development expenditures	6,323	5,259
Financing costs	1,008	1,726
Change in tax rates	51	51
Others	15	26
Total gross deferred tax assets	65,909	53,522
Valuation allowance	(65,909)	(53,522)
Net deferred tax assets	$ —	$ —

The Company files income tax returns in Canada and in the United States. The Company is subject to Canada Revenue Agency and Revenu Québec examination for fiscal years 2017 to 2022 due to unexpired statute of limitation periods and is subject to US Federal and state income tax examination for fiscal years 2019 to 2022.

12 Government assistance

The Company incurred research and development expenditures that are eligible for investment tax credits. The investment tax credits recorded are based on management's estimates of amounts expected to be recovered and are subject to audit by the taxation authorities. These amounts (expressed in thousands of US dollars) have been recorded as a reduction of research and development expenditures the year ended December 31, 2022 and 2021 for an amount of $456 and $458, respectively.

13 Commitments

In the normal course of business, the Company enters into contracts with clinical research organizations, drug manufacturers and other vendors for preclinical and clinical research studies, research and development supplies and other services and products for operating purposes. These contracts generally provide for termination on notice, and therefore are cancellable contracts. Therefore, as at December 31, 2022 there are no contractual commitments, except for office leases (see note 5).

14 Currency risk

The Company is exposed to the financial risk related to the fluctuation of foreign exchange rates and the degree of volatility of those rates. The foreign currency risk is limited to the portion of the Company's business transactions denominated in currency other than US dollars. The following table provides an indication of the Company's exposure to the Canadian dollar, which is expressed in US dollars as of December 31:

	2022	2021
Cash	$ 262	$ 2,049
Other receivables	262	106
Operating lease assets	462	605
Accounts payable and accrued liabilities	(484)	(998)
Operating lease liabilities	(444)	(622)
Net financial position exposure	$ 58	$ 1,140

The Company does not enter into arrangements to hedge its currency risk exposure.

15 Fair value of financial instruments

Pursuant to the accounting guidance for fair value measurement and its subsequent updates, fair value is defined as the price that would be received to sell an asset or paid to transfer a liability (i.e. the exit price) in an orderly transaction between market participants at the measurement date. The accounting guidance establishes a hierarchy for inputs used in measuring fair value that minimizes the use of unobservable inputs by requiring the use of observable market data when available. Observable inputs are inputs that market participants would use in pricing the asset or liability based on active market data. Unobservable inputs are inputs that reflect the assumptions market participants would use in pricing the asset or liability based on the best information available in the circumstances.

The fair value hierarchy is broken down into the three input levels summarized below:

Level 1— Valuations are based on quoted prices in active markets for identical assets or liabilities and readily accessible by the Company at the reporting date.
Level 2— Valuations based on inputs other than the quoted prices in active markets that are observable either directly or indirectly in active markets.
Level 3— Valuations based on unobservable inputs in which there is little or no market data, which requires the Company to develop its own assumptions.

For the years ending December 31, 2022 and December 31, 2021, the Company's fair value hierarchy for all its financial assets was $0, as there were no financial instruments measured at fair value on a recurring basis as of that date.

16 Subsequent Events

On March 22, 2023, we entered into an exchange agreement, or the Exchange Agreement, with entities affiliated with RTW, or the Exchanging Stockholders, pursuant to which the Company exchanged an aggregate of 1,059,000 shares of the Company's common shares owned by the Exchanging Stockholders for pre-funded warrants, or the Exchange Warrants, to purchase an aggregate of 1,059,000 common shares, with an exercise price of $0.001 per share and no expiration date. The Exchange Warrants are exercisable immediately. A holder of the Exchange Warrants (together with its affiliates and other attribution parties) may not exercise any portion of an Exchange Warrant to the extent that immediately prior to or after giving effect to such exercise the holder would beneficially own more than 9.99% of the Company's outstanding common shares immediately after exercise, which percentage may be increased or decreased to any other percentage specified not in excess of 9.99% at the holder's election upon 61 days' notice to the Company subject to the terms of the Exchange Warrants.

On March 27, 2023, the Company entered into certain strategic financing agreements (the "Strategic Financing Agreements") with affiliates of RTW, an existing shareholder, and certain of its affiliates, which will provide up to $125 million in funding to support the development and potential commercial launch of etripamil. Pursuant to the Strategic Financing Agreements, the Company will receive $50 million in exchange for Senior Secured Convertible Notes carrying a 6.0% coupon and having a six-year maturity. Additionally, upon satisfactory FDA approval of etripamil to treat PSVT in adults with expected contradictions, and subject to other customary closing conditions, we will sell our right to receive certain payments on the net sales of products containing etripamil and any forms or formulations of etripamil in the United States of America in exchange for $75 million. Under the Strategic Financing Agreements, RTW will be entitled to receive tiered future payments, based on annual aggregate net sales, as follows: 7% up to $500 million; 4% greater than $500 million and up to $800 million; and 1% above $800 million. RTW is eligible to receive an additional 2.5% for annual aggregate net sales up to $500 million if etripamil does not meet certain annual sales thresholds.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934 (the Exchange Act) that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, control may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

We carried out an evaluation, under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act. Based on this evaluation, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2022.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Rules 13a-15(f) and 15-d-15(f) of the Exchange Act. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

As of December 31, 2022, management assessed and management concluded the effectiveness of internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control – 2013 Integrated Framework (2013 Framework). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2022.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to a transition period established by the JOBS Act for smaller reporting companies.

Inherent Limitations of Internal Controls

Our management, including our principal executive officer and principal financial officer, does not expect that our disclosure controls and procedures or our internal controls will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the company have been detected. These inherent

limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the control. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Changes in Internal Control Over Financial Reporting

During the year ended December 31, 2022, there have been no changes in our internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act, that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

None.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS.

Not applicable.

PART III

Certain information required by Part III is omitted from this report because we will file with the SEC a definitive proxy statement pursuant to Regulation 14A, or the 2023 Proxy Statement, no later than 120 days after the end of our fiscal year, and certain information included therein is incorporated herein by reference.

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this item is incorporated by reference to the information set forth in the sections titled "Proposal No. 1: Election of Directors," "Proposal No. 1: Election of Directors—Information Regarding the Board and Corporate Governance," "Executive Officers," and "Delinquent Section 16(a) Reports," if applicable, in our 2023 Proxy Statement.

Information regarding our Code of Business Conduct and Ethics, or the Code of Conduct, required by this item will be contained in our 2023 Proxy Statement under the caption "Proposal No. 1: Election of Directors—Information Regarding the Board of Directors and Corporate Governance—Code of Business Conduct and Ethics," and is hereby incorporated by reference. If we make any substantive amendments to the Code of Conduct or grants any waiver from a provision of the Code of Conduct to any executive officer or director, we will promptly disclose the nature of the amendment or waiver on its website. The full text of our Code of Conduct is available at the investors section of our website at www.milestonepharma.com. The reference to our website address does not constitute incorporation by reference of the information contained at or available through our website, and you should not consider it to be a part of this Annual Report.

ITEM 11. EXECUTIVE COMPENSATION.

The information required by this item is incorporated by reference to the information set forth in the section titled "Executive Compensation" in our 2023 Proxy.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

The information required by this item is incorporated by reference to the information set forth in the section titled "Security Ownership of Certain Beneficial Owners and Management" in our 2023 Proxy.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE.

The information required by this item is incorporated by reference to the information set forth in the sections titled "Certain Relationships and Related Transactions" and "Proposal No. 1: Election of Directors─Information Regarding the Board of Directors and Corporate Governance─Director Independence" in our 2023 Proxy.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

The information required by this item is incorporated by reference to the information set forth in the section titled "Proposal No. 2: Appointment of Auditor─Auditor Fees" in our 2023 Proxy.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

(a)(1) Financial Statements

See Index to Consolidated Financial Statements on page 103 of this Annual Report on Form 10-K, which is incorporated into this item by reference.

(a)(2) Financial Statement Schedules

All financial statement schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

(b) Exhibits

The following list of exhibits includes exhibits submitted with this Annual Report on Form 10-K as filed with the SEC and others incorporated by reference to other filings.

EXHIBIT NUMBER	DESCRIPTION
3.1	Amended Articles of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on May 15, 2019).
3.2	Amended and Restated Bylaws (incorporated herein by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on May 15, 2019).
4.1	Form of Common Share Certificate (incorporated herein by reference to Exhibit 4.1 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
4.2	Form of Pre-Funded Warrant to Purchase Common Shares (incorporated herein by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 23, 2020.
4.3	Form of Pre-Funded Warrant (incorporated herein by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on October 26, 2020.
4.4	Third Amended and Restated Registration Rights Agreement, by and among the Company and certain of its shareholders, dated October 15, 2018 (incorporated herein by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
4.5	Description of Securities Registered pursuant to Section 12 of the Securities Exchange Act of 1934, as amended
4.6	2021 Inducement Plan, approved by the Board of the Company on November 10, 2021 (incorporated herein by reference to Exhibit 4.10 to the Registrant's Registration Statement on Form S-8 (File No. 333-263807), filed with the SEC on March 24, 2022).
4.7	Form of Exchange Warrant (incorporated herein by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on March 27, 2023).
10.1+	Third Amended and Restated Stock Option Plan (incorporated herein by reference to Exhibit 10.1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.2+	Form of Award and Grant Notices under the Third Amended and Restated Stock Option Plan (incorporated herein by reference to Exhibit 10.2 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.3+	Amended 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38899), filed with the SEC on November 10, 2022).
10.4+	Form of U.S. Stock Option Grant Notice and Stock Option Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.4 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.5+	Form of U.S. Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.5 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).

10.6+	Form of Canadian Stock Option Grant Notice and Option Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.6 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.7+	Form of Canadian Restricted Stock Unit Grant Notice and Restricted Stock Unit Award Agreement under the 2019 Equity Incentive Plan (incorporated herein by reference to Exhibit 10.7 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.8+	2019 Employee Share Purchase Plan (incorporated herein by reference to Exhibit 4.13 to the Registrant's Registration Statement on Form S-8 (File No. 333-231347), filed with the SEC on May 9, 2019).
10.9+	Amended and Restated Employment Agreement between Joseph Oliveto and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.9 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019), as amended by First Amendment to Amended and Restated Employment Agreement between Joseph Oliveto and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.1 to Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.10+	Employment Agreement between Amit Hasija and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on September 9, 2019), as amended by First Amendment to Employment Agreement between Amit Hasija and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.2 to Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.11+	Amended and Restated Employment Agreement between Francis Plat and Milestone Pharmaceuticals Inc. (incorporated herein by reference to Exhibit 10.11 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019), as amended by Amending Agreement between Francis Plat and Milestone Pharmaceuticals Inc. (incorporated herein by reference to Exhibit 10.3 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on June 8, 2020).
10.12+	Employment Agreement, dated February 15, 2022 between David Bharucha, M.D., Ph.D. and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on February 16, 2022).
10.13+	Securities Purchase Agreement dated July 22, 2020 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 23, 2020).
10.14+	Open Market Sale Agreement℠, dated July 29, 2020, by and between Milestone Pharmaceuticals Inc. and Jefferies LLC 2020 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on July 29, 2020).
10.15+	Form of Indemnity Agreement (incorporated herein by reference to Exhibit 10.14 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 12, 2019).
10.16+	Amended and Restated Employment Agreement between Lorenz Muller and Milestone Pharmaceuticals USA, Inc. (incorporated herein by reference to Exhibit 10.12 to Amendment No. 1 to the Registrant's Registration Statement on Form S-1 (File No. 333-230846), filed with the SEC on April 29, 2019).
10.17*	License and Collaboration Agreement by and among the Company and Ji Xing Pharmaceuticals, Limited, dated May 15, 2021 (incorporated herein by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q (File No. 001-38899), filed with the SEC on August 11, 2021.
10.18	Consulting Agreement, between the Company and Francis Plat.
10.19	Non-Employee Director Compensation Policy, as amended.
10.20*	Exchange Agreement, dated as of March 22, 2023, by and among the Company and certain investors party thereto (incorporated herein by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K (File No. 001-38899), filed with the SEC on March 27, 2023).
23.1	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm.
24.1	Power of Attorney (included on the signature page to this registration statement).
31.1	Certification of Principal Executive Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
31.2	Certification of Principal Financial Officer pursuant to Rules 13a-14(a) and 15d-14(a) promulgated under the Securities Exchange Act of 1934, as adopted pursuant to section 302 of the Sarbanes-Oxley Act of 2002

32.1^	Certification of Principal Executive Officer and Principal Financial Officer pursuant to Rules 13a-14(b) and 15d-14(b) promulgated under the Securities Exchange Act of 1934 and 18 U.S.C. Section 1350, as adopted pursuant to section 906 of The Sarbanes-Oxley Act of 2002
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibit 101)

* Certain portions of this exhibit have been omitted pursuant to Item 601(b)(10) of Regulation S-K. The Registrant hereby undertakes to furnish to the SEC, upon request, copies of any such instruments.

\+ Indicates a management contract or compensatory plan

^ These certifications are being furnished solely to accompany this Annual Report pursuant to 18 U.S.C. Section 1350, and are not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and are not to be incorporated by reference into any filing of the Registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

ITEM 16. FORM 10-K SUMMARY

Not applicable

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Company has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Milestone Pharmaceuticals Inc.

Dated: March 29, 2023

/s/ Joseph Oliveto
Joseph Oliveto
Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Joseph Oliveto and Amit Hasija, and each of them, as his or her true and lawful attorneys-in-fact and agents, each with the full power of substitution, for him or her and in his or her name, place or stead, in any and all capacities, to sign any and all amendments to this report, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their, his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Company and in the capacities indicated on the 29th of March 2023.

/s/ Joseph Oliveto Joseph Oliveto	Chief Executive Officer (principal executive officer)
/s/ Amit Hasija Amit Hasija	Chief Financial Officer (principal financial officer and principle accounting officer)
/s/ Robert J. Wills Robert Wills	Chairman of the Board
/s/ Michael Tomsicek Michael Tomsicek	Director
/s/ Paul Truex Paul Truex	Director
/s/ Debra K. Liebert Debra K. Liebert	Director
/s/ Richard Pasternak Richard Pasternak	Director
/s/ Lisa M. Giles Lisa M. Giles	Director

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following description sets forth certain material terms and provisions of the securities of Milestone Pharmaceuticals Inc. (the "Company") that are registered under Section 12 of the Securities Exchange Act of 1934, as amended. The following description of our securities is intended as a summary only and is qualified in its entirety by reference to our articles of incorporation and amendments thereto and our bylaws, each of which are filed as exhibits to the Annual Report on Form 10-K of which this description is a part, and to the applicable provisions of the Business Corporations Act (Québec) (BCA).

General

Our authorized share capital consists of an unlimited number of common shares, no par value per share, and an unlimited number of preferred shares, no par value per share, which are issuable in one or more series.

Common Shares

Voting Rights

Under our articles of incorporation, the holders of common shares are entitled to one vote for each share held at any meeting of our shareholders.

Dividends

Subject to the prior rights of holders of our preferred shares, if applicable, the holders of common shares are entitled to receive dividends as and when declared by our board of directors. We have never declared or paid cash dividends on our share capital, and we do not currently intend to pay any cash dividends on our share capital in the foreseeable future. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business. Any future determination related to dividend policy will be made at the discretion of our board of directors, subject to applicable laws, and will depend upon, among other factors, our results of operations, financial condition, contractual restrictions and capital requirements. In addition, our ability to pay cash dividends on our share capital in the future may be limited by the terms of any future debt or preferred securities we issue or any credit facilities we enter into.

Liquidation

Subject to the prior payment to holders of our preferred shares, if any, in the event of our liquidation, dissolution or winding-up or other distribution of our assets among our shareholders, the holders of common shares are entitled to share *pro rata* in the distribution of the balance of our assets.

Rights and Preferences

The holders of common shares have no preemptive, conversion rights or other subscription rights. There are no redemption or sinking fund provisions applicable to our common shares. There is no provision in our articles of incorporation requiring the holders of common shares to contribute additional capital or permitting or restricting the issuance of additional securities or any other material restrictions. The rights, preferences and privileges of the holders of common shares may be subject to, and adversely affected by, the rights of the holders of any series of preferred shares that we may designate in the future.

Preferred Shares

We do not have any preferred shares outstanding. Under our articles of incorporation, we are authorized to issue, without shareholder approval, an unlimited number of preferred shares, issuable in one or more series, and, subject to the provisions of the BCA, having such designations, rights, privileges, restrictions and conditions, including dividend and voting rights, as our board of directors may determine, and such rights and privileges, including dividend and voting rights, may be superior to those of the common shares. The issuance of preferred shares, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in control of our company and might adversely affect the market price of our common shares and the voting and other rights of the holders of common shares. We have no current plans to issue any preferred shares.

Registration Rights

Holders of certain of the common shares issued upon the conversion of our preferred shares in connection with our initial public offering on May 13, 2019 are entitled to certain rights with respect to registration of any securities held by such investors, as well as any under the Securities Act. These shares are referred to as registrable securities. The holders of these registrable securities possess registration rights pursuant to the terms of our third amended and restated registration rights agreement and are described below. The registration of common shares pursuant to the exercise of the registration rights described below would enable the holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective. We will pay the registration expenses, other than underwriting discounts, selling commissions and share transfer taxes for the shares registered pursuant to the demand, piggyback and Form S-3 registrations described below. Expenses relating to underwriting discounts, selling commissions and share transfer taxes for the shares registered will be borne by us and the participating holders in proportion to the number of common shares sold by each, or, as between the participating holders, as such participating holders may otherwise agree.

Generally, in an underwritten offering, the managing underwriter, if any, has the right, subject to specified conditions, to limit the number of shares the holders may include. The demand, piggyback and Form S-3 registration rights described below will expire upon the earliest of (i) the occurrence of certain mergers or consolidations of the company, (ii) the date on which the shares that are the subject to the agreement are publicly sold, or if they may be publicly sold: (x) pursuant to Rule 144 of the Securities Act and (y) Section 2.5 of Regulation 45-102 respecting Resale of Securities, as adopted by the Canadian Securities Administrators, and (iii) five years after the completion of our initial public offering.

Demand Registration Rights

Certain holders of the common shares issued upon conversion of our preferred shares are entitled to certain demand registration rights. These demand rights permit holders of at least 25% of the registrable securities then outstanding, on not more than two occasions, to request that we register all or a portion of their shares, subject to certain specified exceptions, pursuant to either the Securities Act, Regulation 41-101 respecting General Prospectus Requirements, as adopted by Canadian Securities Administrators or both.

Piggyback Registration Rights

Holders of certain of the common shares issued upon conversion of our preferred shares are entitled to include their shares of registrable securities in any registration statement we file in the event that we propose to register any of our securities under the Securities Act in an offering, either for our own account or for the account of other security holders, subject to specified conditions and limitations.

S-3 Registration Rights

Holders of certain of the common shares issued upon conversion of our preferred shares are entitled to certain Form S-3 registration rights. The holders of at least 25% of the registrable securities then outstanding may, on not more than two occasions within any 12-month period, request that we register all or a portion of their shares on Form S-3 or a form under the Canada-United States Multijurisdictional Disclosure System, or the MJDS, if we are qualified to file a registration statement on Form S-3 or the MJDS, as applicable, subject to specified exceptions. Such request for registration on Form S-3 must cover securities with an aggregate offering price which equals or exceeds$10.0 million. The right to have such shares registered on Form S-3 is further subject to other specified conditions and limitations.

Indemnification

The third amended and restated registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling shareholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Transfer Agent and Registrar

Our transfer agent and registrar for our common shares is Computershare Investor Services Inc., with an address of 1500 Robert-Bourassa Boulevard, 7th Floor, Montréal, Quebec H3A 3S8.

Nasdaq Global Market Listing

Our common shares are listed on The Nasdaq Global Market under the trading symbol "MIST."

Advance Notice Procedures and Shareholder Proposals

Under the BCA, shareholders may make proposals for matters to be considered at the annual general meeting of shareholders. Such proposals must be sent to us in advance of any proposed meeting by delivering a timely written notice in proper form to our registered office in accordance with the requirements of the BCA. The notice must include information on the business the shareholder intends to bring before the meeting.

In addition, our bylaws require that shareholders provide us with advance notice of their intention to nominate any persons, other than those nominated by management, for election to our board of directors at a meeting of shareholders.

These provisions could have the effect of delaying the nomination of certain persons for director that are favored by the holders of a majority of our outstanding voting securities.

Exhibit 10.18

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (the "Agreement") is made and entered into this 8th day of November 2022 and will be effective as of January 1, 2023 (the "Effective Date").

BETWEEN: MILESTONE PHARMACEUTICALS INC., a corporation duly incorporated under the Canada Business Corporations Act, having its headoffice at 6210 Ardrey Kell Rd Suite 650, Charlotte, NC 28277(the "Company")

AND: FRANCIS PLAT, 3 Allée du Puits, B501, 92130, Issy Les Moulineaux (the "Consultant" and together with the Company, the "Parties").

RECITALS:

A. The Consultant has been employed as the Chief Medical Officer (CMO) of the Company pursuant to an Amended and Restated Employment Agreement dated May 8, 2019, as amended by an Amendment Agreement dated June 4, 2020 (together the "Employment Agreement") and in February 2022, transitioned from CMO to Chief Scientific Officer.

B. The Consultant has decided to retire and the Company and Consultant have mutually agreed to the termination of the Employment Agreement and Consultant's employment thereunder effective as of December 31, 2022 (the "Termination Date").

C. The Company desires to retain the Consultant effective January 1, 2023 (the "Effective Date") to provide consulting services to the Company, and the Consultant agrees to provide such services on the terms and conditions set out in this Agreement.

D. In consideration of the Consultant's new role with the Company and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties have agreed to enter into this Agreement, which entirely replaces and supersedes the Employment Agreement as of the Effective Date except as specifically set out herein, and sets out the rights and obligations of the Parties.

THEREFORE, the Parties agree as follows:

The preamble forms integral part of this Agreement.

1. TERM OF AGREEMENT

(a) The term of this Agreement (the "Term") shall commence on the Effective Date and shall continue unless either Party provides thirty (30) days' prior written notice to the other of its/his intention to terminate this Agreement. The Company may also terminate this Agreement immediately and without prior notice if the Consultant refuses to or is unable to perform the Services (as defined below) or is in material breach of this Agreement. The Consultant may terminate this Agreement

immediately and without prior notice if the Company is in material breach of this Agreement.

(b) Upon termination of this Agreement for any reason whatsoever, the Company shall only be responsible for the payment of any reasonable expenditures properly incurred and documented by the Consultant under this Agreement up to the effective date of termination, and for payment of any fees accrued under this Agreement up to the effective date of termination.

2. TRANSITIONAL MATTERS

(a) Notwithstanding the termination of the Employment Agreement, the Consultant shall remain eligible to receive a bonus in respect of the calendar year 2022 pursuant to the Employment Agreement. Any such bonus is to be determined by the Company's Compensation Committee and based on the same methodology as for the other executives of the Company. The Company shall pay the Consultant this bonus, if any, by no later than March 15, 2023. The Company agrees that this obligation will become effective as of the date of this Agreement.

(b) The Consultant currently has options to purchase vested shares of the Company's common stock (the "Options") pursuant to the Company's Stock Option Plan and related grant documents (the "Plan"). Notwithstanding the termination of the Employment Agreement, the vesting of all of the Options shall continue during the Term of this Agreement in accordance with the terms of the Plan. The Consultant's right to exercise the Options shall be as set forth in the Plan, subject to subparagraph (d) below.

(c) Notwithstanding any provision of the Plan to the contrary, upon termination of this Agreement by the Company or its successor other than for Cause (as defined by the Plan), the vesting of all of the Consultant's then-unvested and outstanding Options shall accelerate, and all such Options shall become fully vested. Upon termination of this Agreement by Consultant, or upon termination by the Company for Cause (as defined by the Plan), the vesting of any remaining and outstanding Options shall cease as of the date of such termination. In addition, if there is a Change of Control during the Term of this Agreement all outstanding Options shall become fully vested.

(d) Subject to the insider trading policy of the Company as in effect from time to time as well as applicable securities laws, during the Term of this Agreement, the Consultant shall be entitled to exercise all of his vested Options at any time in his sole discretion up until the tenth anniversary of their date of grant, without any

accelerated expiry or termination of any Option for any reason, notwithstanding any provision of the Plan to the contrary. The Company hereby undertakes to immediately take and implement all measures required under the Plan to ensure the foregoing. Upon termination of this Agreement for any reason, the Consultant will have ninety (90) days to exercise his vested Options.

(e) Any accrued but untaken paid time off will be paid out in the form of compensation in the Consultant's final regular employee paycheck of 2022.

(f) The Consultant's eligibility for and participation as an employee in the Company benefits plans, including medical, dental, vision, retirement, and others, will cease as of the Termination Date, except for any portion of those plans that have vested. Consultant will be provided with additional information regarding these benefit plans prior to the Termination Date.

3. SERVICES TO BE PROVIDED

(a) The Company hereby retains the Consultant to provide scientific advice in his field of expertise including the expected activities and responsibilities as outlined generally in APPENDIX A attached hereto, as well as such other tasks consistent with the medical advisor role as shall be assigned to the Consultant by the Chief Medical Officer of the Company (the "CMO"), or the Chief Executive Officer of the Company (the "CEO") or any designee of the CMO or CEO at any time and from time to time (collectively, the "Services"). Services are only to be undertaken if and to the extent requested by the CMO, the CEO, or a designee of theirs.

(b) The Consultant shall determine the manner and means (including the legal means) by which he provides the Services. The Company grants the Consultant the authority and discretion to do such things as may be reasonably necessary for the purposes of performing the Services. However, the Consultant shall not have the authority or discretion to enter into any agreement, contract or understanding that legally binds the Company or otherwise assume, create, or incur any obligations or liabilities on behalf of the Company, except as expressly provided for in this Agreement, without first obtaining the prior written consent of the Company.

4. FEES

a) In consideration of the Services provided, the Company shall pay to the Consultant consulting fees at the rate of $15,000 per month for Stage 1, with an expectation that Consultant will devote 16 hours per week or 64 hours per 4-week period to providing the Services as outlined in APPENDIX A for Stage 1. For Stages 2 & 3 as outlined in APPENDIX A, Consultant will be paid at an hourly rate of $300 per hour, with the expectation that Consultant will devote 5 hours per week or 2.5 days monthly for the Services outlined for Stage 2, and 8 hours per month or 1 day monthly for the Services outlined for Stage 3. The Company reserves the right to adjust the scope of hours

based on need and business demands but agrees to provide consistent updates to the Consultant regarding anticipated business needs or demands.

b) The Company will reimburse the Consultant for out-of-pocket expenses incurred in the performance of the Services, so long as such expenses are reasonable, itemized, submitted in conjunction with the invoice for the period during which the expenses were incurred, and include detailed backup documentation. If Consultant is required to travel to the United States or Canada, then the Company shall reimburse Consultant for all travel expenses, including business class airfare.

c) The Consultant shall obtain tax registration numbers and shall be responsible for deducting and remitting such amounts to the applicable regulatory authorities. By signing this Agreement, Consultant acknowledges and agrees that Consultant is solely

responsible for payment of all required taxes on the Consulting Fees. Consultant hereby agrees to indemnify and hold the Company harmless from any and all claims, losses, penalties and fees related to or resulting from Consultant's failure to pay taxes in compliance with applicable law.[1]

5. HOURS AND PLACE OF WORK

An estimate of time allotments corresponding to various activities and phase of the project, is included in APPENDIX A. However, the Consultant agrees to be reasonably available to provide the Services to the Company as may be required. The Consultant acknowledges that there may be special circumstances which will require Services to be provided outside standard working hours for which the compensation will remain the same, as provided under Section 4(a). The Services shall generally be provided remotely, but the Consultant agrees to report to an office of the Company, or such other place designated by the Company on reasonable notice at the Company's expense.

6. INDEPENDENT CONTRACTOR

The Consultant is and shall always remain an independent contractor and is not, and shall not represent himself to be an agent, joint venturer, partner, officer, director or employee of the Company. Nothing contained in this Agreement is intended to create nor shall be construed as creating an employment relationship between the Consultant and the Company. The Consultant has sole responsibility, as an independent contractor, to comply with all laws, rules and regulations relating to the provision of Services. The Consultant shall be responsible for deducting all applicable federal and provincial taxes, deductions, premiums, and amounts owing with respect to those fees paid by the Company and remitting such amounts to those governmental authorities as prescribed by law. As an independent contractor, the Consultant shall not be entitled to any employment related benefits. Upon termination of this Agreement by either Party for any reason, the Company shall only be responsible for paying those fees and reimbursing those expenses associated with the Services provided by the Consultant up to and including the termination date.

7. CONFLICT OF INTEREST

The Consultant agrees that, during the Term of this Agreement and for a period of twelve (12) months following the date of termination of this Agreement, except as provided in (a) below, the Consultant will not, within Canada or the United States, operate, be a partner in, be employed by, provide services as an independent contractor, advisor or consultant for, act as an officer or director of, or be financially interested in any business of any person or entity in competition with any business in which the Company or any of its affiliates operates, or develops, sells, provides or distributes competitive goods, products or services, including the paroxysmal supraventricular tachycardia (PSVT), atrial fibrillation and angina programs, or any other business previously evaluated by the Company or any of its affiliates with which the Consultant was involved, including the etripamil program (each such businesses being a "Competitive Business"). Notwithstanding the foregoing, the Consultant shall not be in default under this provision by virtue of:

(a) holding, strictly for investment purposes and as a passive investor, not more than

[1] This last provision may not be permissible or enforceable under Canadian law.

five percent (5%) of the issued and outstanding shares of a Competitive Business, the shares of which are listed on a recognized stock exchange;

(b) any involvement in an undertaking that carries on multiple separate businesses, units or divisions one of which is a Competitive Business, provided the Consultant is not involved in the Competitive Business;

(c) being employed by or providing services to a Competitive Business if such employment or services engagement is not in a Same or Similar Capacity. For the purposes of this Agreement, "Same or Similar Capacity" means: (i) substantially the same or similar capacity or function in which the Consultant worked for the Company or any affiliate at any time during the twelve (12) final months of his relationship with the Company; and/or (ii) any other capacity where he could use his knowledge of confidential information of the Company or its affiliates to provide a competitive advantage to any Competitive Business.

8. NON-SOLICIT

During the Term of this Agreement and for one (1) year after its termination, the Consultant will not directly or indirectly recruit, solicit, or induce any employee of the Company or its subsidiaries to terminate his or her employment with Milestone or its subsidiaries.

9. CONFIDENTIALITY OF INFORMATION AND OWNERSHIP OF PROPRIETARY PROPERTY

The Consultant hereby acknowledges that his post-employment duties and obligations under the Confidentiality of Information and Ownership of Proprietary Property Agreement, dated 8/26/22, attached below in Schedule A of this Agreement (the "Confidentiality Agreement"), will remain in full force and effect in accordance with its terms, and that a breach of the Confidentiality Agreement will constitute a breach of this present Agreement.

10. COMPLIANCE

The Consultant agrees to provide the Services in a competent, efficient, professional, timely and safe manner and always in material compliance with (i) applicable law; (ii) Company policies, rules, systems and procedures as shall be in force; and (iii) the terms of this Agreement.

11. SEVERABILITY

In the event that any covenant, provision or restriction contained in this Agreement is found to be void or unenforceable (in whole or in part) by a court of competent jurisdiction, it shall not affect or impair the validity of any other covenant, provisions or restrictions contained herein, nor shall it affect the validity or enforceability of such covenants, provisions or restrictions in any other jurisdiction or in regard to other circumstances. Any covenants, provisions or restrictions found to be void or unenforceable are declared to be separate and distinct, and the remaining covenants, provisions and restrictions shall remain in full force and effect.

12. CHANGES TO AGREEMENT

Any modification or amendment to this Agreement shall have no force or effect unless in writing

and signed by both Parties.

13. ENUREMENT

This Agreement shall endure to the benefit of and be binding upon the Parties and their respective successors and assigns, including without limitation, the Consultant's heirs, executors, administrators, and personal representatives.

14. ASSIGNMENT

The Consultant may not assign any of the Consultant's rights or delegate any of the Consultant's duties or responsibilities under this Agreement, without the Company's prior written consent. The Company may, without the consent of the Consultant, assign its rights, duties and obligations under this Agreement to an affiliate or to a purchaser of all, or substantially all of the assets of the Company.

15. ENTIRE AGREEMENT

This Agreement (inclusive of the Confidentiality Agreement) constitutes the entire agreement between the Parties and supersedes and replaces any and all other representations, understandings, negotiations and previous agreements, written or oral, express or implied.

16. LEGAL ADVICE

The Consultant acknowledges that the Consultant has read and understands the terms and conditions contained in this Agreement, and that the Company has provided a reasonable opportunity for the Consultant to seek independent legal advice prior to executing this Agreement.

17. CURRENCY

All dollar amounts set forth or referred to in this Agreement refer to US currency.

18. NOTICES

18.1 Notice to Consultant

Any notice required or permitted to be given to the Consultant shall be deemed to have been received if delivered personally to, mailed by registered mail, or sent to 351 Rang Double, St-Urbain-Premier, Quebec J0S 1Y0, or if emailed to the Consultant's then-current personal or active Company-provided email address.

18.2.1 Notice to Company

Any notice required or permitted to be given to the Company shall be deemed to have been received if delivered personally to, mailed by registered mail, or sent to 1111 Dr. Frederik-Philips Blvd., Suite 420, Montréal, Québec, H4M 2X6, addressed to the attention of the CEO, or if emailed to the CEO and CFO of the Company.

19. BINDING EFFECT; WAIVER OF BREACH

Consultant acknowledges and agrees that his obligations under Sections 6, 7, 8 and 9 of this Agreement will survive the termination of this Agreement regardless of the cause or manner of the termination. Any waiver by the Company of a breach of any provision of this Agreement will not operate as a waiver of any subsequent breach of that provision or any other provision of this Agreement.

20. GOVERNING LAW

This Agreement shall be interpreted and construed in accordance with the laws of the Province of Quebec and the laws of Canada applicable therein.

21. LANGUAGE

The Parties hereto have expressly required that this Agreement and documents ancillary thereto be drafted in the English language. *Les Parties à la présente ont expressément exigé que le présent accord et les documents afférents soient rédigés en langue anglaise*.

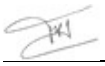
22. COUNTERPARTS

This Agreement may be executed by the Parties in counterparts and the counterparts may be executed and delivered by electronic means, with all the counterparts together constituting one agreement.

IN WITNESS OF WHICH the Parties have duly executed this Agreement:

MILESTONE PHARMACEUTICALS INC.

By:
Name: Joseph Oliveto
Title: Chief Executive Officer
Date:



FRANCIS PLAT
Date: Nov 8, 2022

Appendix A

Expected Scope of work for Francis Plat, MD associated with Consulting Agreement

The following list of potential tasks are meant to be a guideline to provide context to the collaboration and allow both parties to align on high level expectations. They are not to be used as formal approval of duties. Actual work tasks will be directed by Chief Medical Officer or the Chief Executive Officer or their designee and agreed with the Consultant. A general sense of time needs is also provided as an estimate for planning and basic alignment purposes and should not be interpreted as a commitment.

Stage 1 - Period between January 1, 2023 and PSVT NDA Submission

- Final reviewer of critical documents to the dossiers (e.g., RAPID CSR, RAPID-Extension CSR, NODE-303 CSR, Integrated Summary of Efficacy; Integrated Summary of Safety [ISS]); Summary Modules 2.5, 2.7)
- Early consultation on above CSRs and ISS, particularly regarding potential need to review specific cases, special safety issues or designated data analyses.
- Input arising from issues regarding NODE-303 conduct or from study close-outs (e.g., (review clinical case questions or provide consult for internal meetings). Aim is for potential input to be given in focused internal meetings and not regular attendance at larger-group or team meetings.
- Participation in meetings with FDA or EMA as designated and in select internal preparatory meetings
- Final reviewer of select publications
- Select Clinical, Medical Affairs, or Business Development support activities including related to work in the EU.
- For this stage we would anticipate an average of 16 hours per week (e.g., average of 2 days per week) for the remainder of Stage 1, potentially ranging from 40 hours for some weeks and no activity other weeks.

Stage 2 – Period between NDA filing and US approval

- Final reviewer of critical documents to the EMA dossier (e.g., CSRs not in above Stage and EMA Summary documents)
- Participation in meetings with FDA or EMA as designated and select internal preparatory meetings
- Help (review responses or provide consult in internal meetings) responding to select questions received from FDA
- Should we have an Advisory Committee Meeting – we would have a specific discussion and agreement on a role and scope of work and level of commitment to that project. Depending on the approach and role, a separate agreement may be necessary for that project.
- Final review of select publications
- Select Clinical, Medical Affairs or Business Development Support Activities including related to work in the EU. Anticipate that BD activities would focus on the integration of data on potential asset and disease-landscape information.
- For this stage we would anticipate an average of 5 hours per week (e.g., 2.5 days per month), potentially ranging from 40 hours for some weeks and no activity other weeks.

Stage 3 – Period following NDA approval

- Help (review responses or provide consult in internal meetings) responding to select questions from EMA or other Regulatory bodies.
- Participation in EMA or other Regulatory meetings and select internal preparatory meetings
- Final review of select publications
- Select Clinical, Medical Affairs or Business Development Support Activities including related to work in the EU.

- For this stage we would anticipate an average of 8 hours per month (e.g., 1 day per month) with more sporadic interactions compared to prior stages.

Travel - Most activities are expected to be performed remotely through written correspondence, or for meetings by video or telephone conferencing. Travel for in person meetings may be requested for critical meetings or where it would be efficient for Francis to attend (e.g., France or EU)

EXHIBIT 10.19

MILESTONE PHARMACEUTICALS INC.

AMENDED AND RESTATED NON-EMPLOYEE DIRECTOR COMPENSATION POLICY

Each member of the Board of Directors (the "***Board***") of Milestone Pharmaceuticals Inc. (the "***Company***") who is not also serving as an employee of the Company or any of its subsidiaries (each such member, an "***Eligible Director***") will receive the compensation described in this Non-Employee Director Compensation Policy (this "***Policy***"). An Eligible Director may decline all or any portion of his or her compensation by giving notice to the Company prior to the date cash is to be paid or equity awards are to be granted, as the case may be. This Policy may be amended at any time in the sole discretion of the Board or the Compensation Committee of the Board.

Annual Cash Compensation

The annual cash compensation amount set forth below is payable to Eligible Directors in equal quarterly installments, payable in arrears on the last day of each fiscal quarter in which the service occurred. If an Eligible Director joins the Board or a committee of the Board at a time other than effective as of the first day of a fiscal quarter, each annual retainer set forth below will be pro-rated based on days served in the applicable fiscal year, with the pro-rated amount paid for the first fiscal quarter in which the Eligible Director provides the service, and regular full quarterly payments to be paid thereafter. All annual cash fees are vested upon payment.

1. Annual Board Service Retainer:
    a. All Eligible Directors: $35,000
    b. Non-executive chairperson of the Board: $65,000 (inclusive of Annual Board Service Retainer)
2. Annual Committee Member Service Retainer:
    a. Member of the Audit Committee: $7,500
    b. Member of the Compensation Committee: $6,000
    c. Member of the Nominating and Corporate Governance Committee: $4,000
    d. Member of the Clinical Affairs Committee: $6,000
3. Annual Committee Chair Service Retainer (inclusive of Committee Member Service Retainer):
    a. Chairperson of the Audit Committee: $15,000
    b. Chairperson of the Compensation Committee: $12,000
    c. Chairperson of the Nominating and Corporate Governance Committee: $8,000
    d. Chairperson of the Clinical Affairs Committee: $12,000

The Company will also reimburse each of the Eligible Directors for his or her travel expenses incurred in connection with his or her attendance at Board and committee meetings. Such reimbursements shall be paid on the same date as the annual cash fees are paid.

Equity Compensation

The equity compensation set forth below will be granted under the Company′s 2019 Equity Incentive Plan (the "***Plan***"), subject to the approval of the Plan by the Company's shareholders. All stock options granted under this Policy will be nonstatutory stock options, with an exercise price per share equal to 100% of the Fair Market Value (as defined in the Plan) of the underlying common stock on the date of grant, and a term of 10 years from the date of grant (subject to earlier termination in connection with a termination of service as provided in the Plan).

1. Initial Grant: For each Eligible Director who is first elected or appointed to the Board following the effective date of this Policy, on the date of such Eligible Director's initial election or appointment to the Board (or, if such date is not a market trading day, the first market trading day thereafter), the Eligible Director will be automatically, and without further action by the Board or Compensation Committee of the Board, granted a stock option to purchase a number of shares of the Company's common stock equal to 42,000 shares of the Company's common stock. The shares subject to each such stock option will vest monthly over a three-year period, subject to the Eligible Director's Continuous Service (as defined in the Plan) on each vesting date.

2. Annual Grant: On the date of each annual shareholder meeting of the Company held after the Effective Date, each Eligible Director who continues to serve as a non-employee member of the Board following such shareholder meeting will be automatically, and without further action by the Board or Compensation Committee of the Board, granted a stock option to purchase 25,000 shares of the Company's common stock (the "Annual Grant"). The shares subject to the Annual Grant will vest in equal monthly installments over the 12 months following the date of grant, provided that the Annual Grant will in any case be fully vested on the date of Company's next annual shareholder meeting, subject to the Eligible Director's Continuous Service (as defined in the Plan) through such vesting date and will vest in full upon a Change in Control (as defined in the Plan).

Approved: April 26, 2019

Effective: May 8, 2019

Amended: May 4, 2020

Amended: September 21, 2020

Amended and Restated: March 24, 2021

Amended and Restated: February 14, 2023

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-8 (Nos. 333-231347, 333-236971 and 333-254838) of Milestone Pharmaceuticals Inc. of our report dated March 29, 2023, relating to the consolidated financial statements, which appears in Milestone Pharmaceuticals Inc.'s Annual Report on Form 10-K for the year ended December 31, 2022.

/s/PricewaterhouseCoopers LLP
Montréal, Canada
March 29, 2023

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Joseph Oliveto, certify that:

1. I have reviewed this Annual Report on Form 10-K of Milestone Pharmaceuticals Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 29, 2023

/s/ Joseph Oliveto
Joseph Oliveto
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Amit Hasija, certify that:

1. I have reviewed this Annual Report on Form 10-K of Milestone Pharmaceuticals Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 29, 2023

/s/ Amit Hasija
Amit Hasija
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Joseph Oliveto, Chief Executive Officer of Milestone Pharmaceuticals Inc. (the "Company"), and Amit Hasija, Chief Financial Officer of the Company, each hereby certifies that, to the best of his or her knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2022, to which this Certification is attached as Exhibit 32.1 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 29, 2023

/s/ Joseph Oliveto	/s/ Amit Hasija
Joseph Oliveto	Amit Hasija
Chief Executive Officer	Chief Financial Officer
(Principal Executive Officer)	(Principal Financial and Accounting Officer)